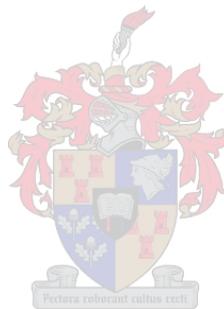


Association Between Motor Timing and Treatment Outcomes in Patients with Alcohol and/or Cocaine Addiction in a Rehabilitation Programme.

by

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Dissertation presented for the degree of Doctor of Philosophy in the Faculty of Medicine and Health Sciences at University of Stellenbosch



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Declaration

I, Susanne Yvette Young, the undersigned hereby declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously, in its entirety or in part, submitted it for obtaining any qualification.

This dissertation includes one original paper published in a peer-reviewed journal and five unpublished publications. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and, for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

Signature

Date: December 2017

*“Time has the ineffable character that reveals its existence only
through a construct of the mind”*

-Kant, 1845

Summary

Introduction Motor timing deficits have been found in DA system related disorders and, more recently, also in individuals with Substance Use Disorders (SUD). Motor timing is fundamental to our ability to coordinate movements and is defined as a component of temporal brain processing. Modifications to neural systems associated to these domains contribute to motor timing deficits and pathology; however, the underlying mechanisms that lead to these deficits are still poorly understood. A bimodal distribution and evolutionary neurobiological model may provide a useful pathogenic framework for the classification of major psychiatric disorders, including SUD. In this model, major psychiatric disorders (including SUD) may be understood as progressive manifestations of imbalances between dual neural circuitries in the brain. These include an automatic mechanism (referred to as the Drive Mechanism, DM) and a more cognitive-predictive mechanism (referred to as the Guidance Mechanism, GM). To our knowledge, motor timing has not been investigated in populations with SUDs with regard to treatment outcome and relapse. The main question of this study was: Do imbalances between the DM and GM, as expressed in motor timing deficits, differentiate individuals with SUD from normal controls and predict poorer treatment response and relapse? **Methods** This study investigated motor timing and its relation to treatment response and relapse in individuals with Alcohol and/or Cocaine Use Disorder (AUD and/or CUD) compared to a Healthy Control (HC) group. Owing to the novelty of the motor task battery, the tested sensitivity values of motor timing parameters were assessed on test retest variability. The possible confounding effects of attention and working memory on motor timing paradigms, and the high impulsivity levels found in individuals with SUD were addressed by comparing the motor task paradigms with a battery of neuropsychological tests. **Results** Motor timing was found to be predictive of treatment outcomes at 8 weeks. Synchronisation abilities were predictive, but decision making and motor planning abilities were not predictive. Owing to the small size of the follow up sample, a prediction of motor timing with regards to relapse at 12 months was not possible. Motor timing improved with prolonged abstinence. Specifically, synchronisation abilities improved. Decision making and motor planning abilities did not improve over time. Motor timing performance found in our AUD and/or CUD population only partially supported van Hoof's proposed model. However, no deficits were found in internal clock rates or the capacity to plan and coordinate actions. Deficits were found in decision making (DM) and synchronisation abilities (GM) in patients versus HC. Decision making abilities were poorer in CUD compared to AUD. No correlation was found between motor timing and impulsivity. Working memory and attention were found to be predictive of motor timing. Robust test-retest reliability of the test battery was found. **Discussion** These findings provide partial support for the deficits in neurocircuitry, as proposed by van Hoof. Additionally, the findings show that

motor timing holds prognostic for recovers with prolonged abstinence. These findings may have significant implications for future studies and warrant further investigation in SUD populations going forward.

Opsomming

Inleiding Kognitiewe aandagtekort, impulsiwiteitswerkgeheue is by individue met 'n middelgebruikstoornis (MGS; SUD in Engels) gevind en is aanduiders van slegte uitkomst in die behandeling van MGS en terugvalling. Motoriesetydsberekenningsgebreke is ook in stoornisse wat verband hou met die dopamienstelsel en, meer onlangs, by individue met MGS geïdentifiseer. Motoriese tydsberekening lê ten grondslag van ons vermoë om bewegings te koördineer, word gedefinieer as 'n komponent van temporale breinprosessering én korreleer met aandag-, impulsiwiteits- en werksgeheuegebreke. Veranderinge aan die senustelsels wat met hierdie areas geassosieer word dra by tot motoriesetydsberekenningsgebreke en -patologieë, hoewel die onderliggende meganismes wat tot hierdie gebreke lei nog nie voldoende verstaan word nie. 'n Bimodale verspreidings- en evolusionêre neurobiologiese model kan moontlik 'n bruikbare patogeniese raamwerk vir die klassifikasie van die vernaamste psigiatriese stoornisse bied – insluitende MGS. Volgens hierdie model kan die vernaamste psigiatriese stoornisse (insluitende MGS) verstaan word as progressiewe manifestasies van wanbalanse tussen dubbele neurale baanwerke in die brein. Dit sluit 'n outomatiese meganisme (genaamd die drifmeganisme of DM) en 'n kognitief-voorspellende meganisme (genaamd die leidingsmeganisme of LM; GM in Engels). So ver ons kennis strek is motoriese tydsberekening nog nie in populasies met MGS ondersoek met betrekking tot behandelingsuitkomst en terugvalling nie. Die hoofvraag van hierdie studie was: Doen wanbalanse tussen die DM en GM wat in motoriese tydsberekeninge uitgedruk word, onderskei individue met SUD van normale beheermaatreëls en voorspel swakker behandelingsreaksie en terugval? **Metode** Hierdie studie ondersoek motoriese tydsberekening en die verband met behandelingsrespons en terugvalling in individue met alkohol- en/of kokaïnegebruikstoornis (AGS en/of KGS), vergeleke met 'n gesonde kontrolegroep (GK; HC in Engels). Daarbenewens is steun vir die eerder wordende manifestasies van wanbalanse tussen DM en LM ook ondersoek. Gesien die nuttheid van die battery motoriese take is die getoetsde sensitiwiteitswaardes van die parameters vir motoriese tydsberekening op grond van toets-hertoets-veranderlikheid geassesseer. Die moontlike strengel-effek wat aandag en werksgeheue op motoriesetydsberekenningsparadigmas kan hê sowel as die hoë impulsiwiteitsvlakke van diegene met MGS is verreken deur die motoriesetydsberekenningsparadigmas met 'n battery neurosielkundige toetse te vergelyk. **Resultate** Daar is bevind dat motoriese tydsberekening kan voorspel wat die behandelingsuitkomst op agt weke sal wees. Sinkroniseringsvermoëns was voorspellend, maar nie besluitnemings- en motoriesebeplanningsvermoëns nie. Weens die beperkte grootte van die steekproef tydens die opvolgondersoek, was dit nie moontlik om te voorspel of daar op 12 maande terugsakking sou wees wat motoriese tydsberekening betref nie. Daar is bevind dat

motoriese tydsberekening met langdurige onthouding verbeter. Sinkroniseringsvermoëns het veral verbeter. Besluitnemings- en motoriesebeplanningsvermoëns het nie mettertyd verbeter nie. Die motoriese tydsberekeningsprestasie wat by MGS-deelnemers bevind is, ondersteun ten dele Van Hoof se model. DM-wanbalanse wat op verhoogde interne chronometergang en/of die vermoë om handeling te beplan en te koördineer, gebaseer is, is nie deur die data ondersteun nie. Gemeet aan besluitneming (DM) en sinkroniseringsvermoëns (LM) in pasiënte (teenoor GK), is daar bevind dat DM effens beter funksioneer vergeleke met LM. Daarbenewens is sterker DM-funksionering relatief tot GM in KGS gevind ten opsigte van besluitnemingsvermoëns – in teenstelling met AGS. . Daar is geen beduidende korrelasies gevind tussen die prestasies in die motoriese take en metings vir impulsiewe keuses en snelreaksieimpulsiwiteit in die neurosielkundigetoetsbattery nie. Daar is gevind dat visuele en ouditiewe werksgeheue en aandag ten dele voorspellend is vir motoriese tydsberekening, maar slegs met verhoogde taakkompleksiteit. Laastens is sterk toets-hertoets-betroubaarheid vir die impulsiwiteitstoetsbattery in alle motoriesetydsberekeningstake gevind. **Bespreking** Hierdie bevindinge bied gedeeltelike steun vir gebreke in neurobaanwerke, soos deur Van Hoof voorgestel. Daarbenewens toon hierdie bevindinge ook dat motoriese tydsberekening prognostiese waarde inhou vir motoriese tydsberekening in MGS sowel as vir hersteltekens met langdurige onthouding. Hierdie bevindinge hou beduidende implikasies in vir toekomstige studies. Motoriese tydsberekening behoort in nuwe navorsingsparadigmas oorweeg te word.

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List of Abbreviations

SUD	Substance Use Disorder
AUD	Alcohol Use Disorder
CUD	Cocaine Use Disorder
DA	Dopamine
PFC	Pre Frontal Cortex
EHQ	Edinburgh Handedness Questionnaire,
MATE 2.10	Measurements in the Addictions for Triage and Evaluation 2.10
MINI	Mini International Neuropsychiatric Interview
AUDIT	Alcohol Use Disorder Identification Test
DUDIT	Drug Use Disorder Identification Test
SDS	Sheehan Disability Scale
AASE	Alcohol Abstinence Self-Efficacy Scale
CASE	Cocaine Abstinence Self-Efficacy Scale
BDI	Beck Depression Inventory
BIS-11	Barratt Impulsiveness Scale Version 11
TMT	Trail Making Test
LNS	Letter- Number Sequencing Task
IGT	Iowa Gambling Task
ISI	Inter Stimulus Interval
IRI	Inter Response Interval
IRI Error	Inter Response Interval Error
Asynchrony	Synchronisation Error
CT	Contact Time
SE	Spatial Error

IC	Impulsive Choice
RRI	Rapid Response Impulsivity
AUD	Alcohol Use Disorder
CUD	Cocaine Use Disorder
GM	Guidance Mechanism
DM	Drive Mechanism

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1 Introduction

1.1 Background

Substance Use Disorder (SUD) is associated with dopaminergic dysregulation, dysfunction of fronto-cortical (orbitofrontal cortex and nucleus accumbens), memory (amygdala, hippocampus, thalamus) circuits and marked disruption in brain reward mechanisms. Indeed, chronic cocaine and alcohol administration impact judgement, increase craving, impair salience for natural rewards, increase compulsion, decrease judgement, motivation, and self-control, and increase the risk of relapse (Goldstein et al., 2009; Goldstein & Volkow, 2011; Volkow & Baler, 2014; Volkow, Fowler, & Wang, 2004). Cocaine, and indirectly alcohol abuse, have consistently been associated with cognitive-executive impairments (Potvin, Stavro, Rizkallah, & Pelletier, 2014; Stavro, Pelletier, & Potvin, 2013).

There is some consensus in the neuroscientific literature that SUD is the result of an imbalance between two neural circuitries in the brain - an automatic and a reflective system (Bechara, 2005; Tiffany, 1990; Wiers et al., 2007). These circuitries are believed to be separate but competing (Bechara, 2005; Volkow et al., 2004; Volkow, Wang, Tomasi, & Baler, 2013). The automatic system, a bottom-up system, acts on cues of pleasure or pain, in an immediate fashion without regarding long term consequences. The reflective system on the other hand, a top down (frontal lobe) system, acts on pain or pleasure in a future oriented way. Especially the pre-frontal cortices which have been involved in a widespread range of executive and self-control functions believed to involve the reflective system (Volkow et al. 2010; Volkow et al. 2013; Bechara 2005; Cohen & Lieberman 2010). In healthy individuals, these two neuro-circuitries are balanced; the automatic system is controlled by the reflective

system through a range of mechanisms. Examples of these mechanisms are the ability to suppress undesired thoughts and premature actions, inhibit impulsive responses or disadvantageous decision making (Bechara & Van Der Linden 2005; de Wit 2009). In SUD, this control is believed to be diminished resulting from a hyperactivity of the automatic system, which overrides the reflective system's ability to assert control, which affect long-term outcomes (Bechara, 2005). Repeated stimulation of the dopamine (DA) pathway, associated with the use of addictive substances, triggers neurobiological adaptations in neural transmission, and plasticity changes in glutamatergic cortico-striatal pathways (Volkow, Wang, Fowler, & Telang, 2008). As such, the associated experience of 'loss of control' in SUDs can be explained through neurobiological adaptations in downstream circuits (Bechara, 2005; Volkow et al., 2010).

Besides cognitive-executive impairments, temporal processing deficits are shared in a range of otherwise distinct disorders associated with DA dysfunction (e.g. Schizophrenia and SUD) (Avanzino et al., 2016; Avanzino, Pelosin, Martino, Abbruzzese, & Maurits, 2013; Berlin & Rolls, 2004; Coull, Cheng, & Meck, 2011; Delevoye-Turrell, Giersch, Wing, & Danion, 2007; Delevoye-Turrell, Wilquin, & Giersch, 2012; Drew et al., 2007; Moreira, Pinto, Almeida, & Barbosa, 2016; Rao et al., 1997; Volkow et al., 2004). A component of temporal processing, motor timing, regulates the generation of timed motor responses (Mauk & Buonomano, 2004) and underpins self-initiated movement sequences (Bortoletto, Cook, & Cunnington, 2011) and sensory motor synchronisation (Repp & Su, 2013), and is inextricably related to motor control (Mauk & Buonomano, 2004; Raghavan, Prevosto, & Sommer, 2016).

Despite the potential importance of temporal processing in psychopathology, and SUD specifically, little attention has been given to the study of motor timing

abilities (Coslett, Shenton, Dyer, & Wiener, 2009; Moreira et al., 2016). The precise way in which implicated pathogenic mechanisms underlie the deficits in the SUDs remains unclear, however research points to aetiological evolutionary, developmental, and genetic influences (Goldstein et al., 2009; Goldstein & Volkow, 2011; Kalivas, Volkow, & Seamans, 2005; Wise, 2000). In addition, theoretical models that enhance interdisciplinary understanding of SUD are lacking.

1.2 A bimodal distribution and evolutionary neurobiological model for SUD

Van Hoof argues that SUDs can be explained through evolutionary and developmental processes, and that a bimodal distribution and evolutionary neurobiological model may provide a useful pathogenic framework for the classification of major psychiatric disorders, including SUDs (van Hoof, 2003; Van Hoof, 2002). The model proposes that during phylogenesis and ontogenesis brain mechanisms from motoric to limbic areas are effected in a repetitive way. The model explains that the motoric mechanisms necessary for grasping stationary and moving objects evolved and matured to organize cognitive and emotional processes, such as affiliation and intimidation. This organisational process resulted in the capacity to organize intentional behaviour (van Hoof, 2002; 2003). Thus, mental representations of intended or goal-action effects are responsible for the planning and execution of appropriate movements required to achieve a goal (van Hoof, 2002; 2003). In the general population, individual trait differences come into effect through relative strengths and weaknesses in the development of these mechanisms. Individual trait differences in healthy populations are expressed through an innate bimodal distribution of the personality traits of extraversion and introversion.

Following this model, major psychiatric disorders (e.g., schizophrenia and SUDs) may be understood as manifestations of imbalances between an automatic mode of action (referred to as the Drive Mechanism) and a more cognitive-predictive mode of action (referred to as the Guidance Mechanism, GM). The DM is based upon the compilation of stimulus–response rules specifying the motor routines that action-relevant objects habitually require (sensorimotor learning) and is thought to be controlled by a circuit that includes the parietal cortex, the ventral premotor cortex and the basal ganglia; ii) the GM, is a more cognitive-predictive mode of action, based on a compilation of action–effect rules specifying the actions and effects produced and is mediated by frontal striatal circuits. The GM includes the dorsolateral prefrontal cortex, anterior cingulate, and the cerebellum (van Hoof, 2002; 2003). This model attempts to provide an integrative explanatory model of psychopathology by combining multiple theories and disciplines. This model fits well with the theory of ‘embodied cognition’. With ‘embodied’ cognition we refer to the idea that cognition depends on bodily morphology and subtle environmental cues (Thompson, Sameen, & Racine, 2016). The major influences on this model are briefly described below.

1.3 Movement, cognition and the cerebellum: Embodied cognition

Van Hoof’s model fits in well with the theory that cognition is embodied. Embodied cognition, a post cognitive approach, supports the view that the cognitive system is highly dependent on sensory motor processes(Thompson et al., 2016). It proposes that representations are multimodal and thus fundamentally grounded in sensorial modalities of the brain (Wilson, Golonka, & Hesslow, 2002). As such, due to its dependence on sensory motor processes, higher cognition is believed to make up an

intrinsic part of these processes (Barton, 2012; Thompson et al., 2016; Wilson et al., 2002). Current neuroscientific research does not approach the working of the brain as a whole, and dominant models of brain functioning mostly apply a 'top-down' approach and fail to consider the roles of subcortical structures (Koziol, Budding, & Chidekel, 2012). There is some disagreement in the literature with this approach as in order for a person to function adaptively the same sensory motor circuits responsible for the processing of sensory information, such as information associated with reward values, also process the execution of higher cognitive functions, such as decision making (Barton, 2012, Koziol et al., 2012). This is what allows a person to function adaptively (Koziol et al., 2012). As such, cognition is best understood as the elaboration of specialized intrinsic systems of adaptive control, in which the cerebellum, specifically, plays an important role, due to its crucial role in planning and executing actions (Barton, 2012).

1.4 Human action

The generation of human actions represent a complex interaction of cognitive, visual and proprioceptive information: in order to act we need to select the effector, conduct an action, whilst simultaneously determining the target for that action. We plan in order to reach goals, and our perception guides us with regards to the proximity of reaching these goals (Haggard, Clark, & Kalogeras, 2002). Actions unfold over time and through a complex sequence of internal events. These sequences reflect the making and execution of behavioural plans which become vastly complex, since we, as humans, are able to correct current and future plans and the execution thereof based on re-afferent feedback allowing for adjustment to our actions. A considerable body of research indicates that specific neuronal pathways in the brain coordinate

intentional behaviour even though the way these actions are manifested by the body are the same in terms of muscle activity, observed kinematics, and dynamics and that these pathways regulate both intentional cognitive and motor actions (Haggard et al., 2002). There is good evidence indicating that two specific neuronal pathways in the brain coordinate goal directed movements (Herwig, Prinz, & Waszak, 2007; van Hoof, 2003; Van Hoof, 2002). These are thought to consist of an; i) automatic circuit that aims to control action in response to environmental input (stimulus based actions), and ii) a reflective circuit which is thought to guide actions by internal representations (representation based actions) (Filevich, Kühn, & Haggard, 2012; Haggard et al., 2002; Van Hoof, 2002). Imbalances in these routes to action are hypothesised to be mediated by automatic processes leading to aversive health outcomes (Strack & Deutsch, 2004). However, little is known about what happens on these routes to action (Herwig et al., 2007). What we do know is that plans designed to achieve a goal through movement depend on neural processes comprised of perceptual and motor aspects (Haggard et al., 2002). We plan an action in order to reach goals and our perception of these actions guide us with regards to the proximity of reaching these goals. Action leaves behind an association between the action's motor code and the sensory effects the action produces (action–effect binding). These associations are bidirectional and can thus be used to retrieve an action by anticipating its effects. In other words, representation-guided actions are selected with respect to their perceptual consequences (Haggard et al., 2002; Hommel, 2003; Prinz, 1997). Thus, mental representations of intended action effects are can be used for the planning and execution of the appropriate movements to achieve a goal (Filevich et al., 2012; Haggard et al., 2002; Hommel, 2003; Prinz, 1997). It has been argued that this action-effect binding occurs due to the integration

of underlying perceptual and motor codes which are bound together in a common representational domain (Hommel, 2003).

1.5 The neurobiology of timed behaviours

Novel research suggests that the timing of behaviour is not solely influenced by kinematic or peripheral properties but by movement-specific sensory feedback, meaning that timing processes do, in fact, reflect perceptual goals (Iversen & Balasubramaniam, 2016). The capacity to accurately detect and understand the intentions of others, anticipate their upcoming actions, and appropriately adjust one's own behaviour are fundamental to our ability to interact as humans (Gallese, Rochat, Cossu, & Sinigaglia, 2009). Since all actions and perceptions have by default temporal and spatial dimensions the neural mechanisms underlying the brain's ability to measure time, and act on it, are a focus of increased research interest (Lewis & Miall, 2003). Given the intricate link between temporal and spatial information in our environment, the processing of time and space are believed to be fundamental properties of neural functioning (Mauk & Buonomano, 2004).

Timed behaviours are coordinated by neural systems regulated by the dopamine (DA) system and its target neural substrates (Striatum and PFC) (Brighthouse et al., 2013; Soares, Atallah, & Paton, 2016; Wittmann & Paulus, 2008). Millisecond timing is crucial for speech generation and recognition, motor control and dancing, and depends on an intact striatum, but is not dependent on an intact suprachiasmatic nucleus or cerebellum. However, during interval timing both the striatum and cerebellum become activated, indicating possible joint coordination of different aspects of timing (Buhusi & Meck, 2005). Research on explicit judgement

and motor timing has found that the cerebellum plays a crucial role in discontinuous movements when brief time intervals are a core component (Grondin, 2010), and has a computational role in timing tasks (Wittmann et al., 2011). The frontal lobes on the other hand are believed to play a crucial role in the coding of temporal information, the (posterior) parietal cortex in the processing of temporal intervals, and the basal ganglia in the processing of temporal information (Grondin, 2010; Wittmann et al., 2011).

Timing systems involve the integration of cortical circuits with the basal ganglia, cerebellum and hippocampus, which support temporal cognition and motor skill learning (Doya, 2000; Lusk, Petter, MacDonald, & Meck, 2016). Accurate cognitive control requires the recruitment of neuroanatomical and functional components of time perception, and performances on timing tasks have been shown to be sensitive measures of deficits in neural mechanisms and cognitive functioning (Suh, Kolster, Sarkar, McCandliss, & Ghajar, 2006). Modifications to these neural systems contribute to (sub-second range) motor timing deficits and pathology involving disruptions in functioning of the cerebellum, PFC, basal ganglia, and hippocampus (Brighthouse et al., 2013; Buhusi & Meck, 2005; Comte et al., 2014; De Corte & Matell, 2016; Gallese et al., 2009; Lewis & Miall, 2003; Soares et al., 2016). Indeed, the basal ganglia (dorsal striatum) does not only play a crucial role in DA transmission (Kalivas et al., 2005) but has also been identified as the brain's context-independent specialized timing system (Coull et al., 2011; Ivry & Spencer, 2004).

A recent review of the timing literature described a clear dissociation in brain activity, related to timing abilities, between two distinct systems of timing; an automatic and cognitive system (Lewis & Miall, 2003). Cerebral controlled event timing, which required the existence of discrete events defining the timing task and a

contrasting emergent timing system for which timing emerges from movements of effectors and is not controlled by cerebral resources (Iversen & Balasubramaniam, 2016; Lewis & Miall, 2003). As such, timing can be seen as a fundamental neuropsychological domain, with broad influence on cognitive functioning. It mediates behavioural and cognitive processes as a basic unit of ability (Allman & Meck, 2012), ranging from goal directed behaviour (Alústiza, Radua, Pla, Martin, & Ortuño, 2017) to basic motor coordination (Buonomano, 2007).

1.6 Linking timing and cognition: evolution and development of the brain

In evolutionary and developmental terms, the ability to anticipate, delay gratification, exercise self-control, is vital not only to survival only but also aids us to thrive and evolve (Gallese et al., 2009; Neufang, Fink, Herpertz-Dahlmann, Willmes, & Konrad, 2008; J. R. Stevens et al., 2007). Timing abilities play a critical role in our behaviour. Timing and time perception and the ability to synchronise with external rhythms are crucial for goal reaching and survival in both animals and humans and are thought to be implicated in a range of behaviours (Buhusi & Meck, 2005; M. Wilson & Cook, 2016). Motor timing, specifically, is fundamental to our ability to coordinate movements and is defined as a component of temporal brain processing (Mauk & Buonomano, 2004). The importance of timing is illustrated by the fact that the basic mechanisms involved in these processes developed early in evolution and have been conserved (Coslett et al., 2009). Furthermore, there is ever growing evidence from developmental psychology that experience based motor knowledge shapes the development of social cognitive skills (Gallese et al., 2009). The early developmental emergence of timing abilities and their stability across stages of child development demonstrate that the brain is equipped with a temporal processing system from birth

(Droit-Volet, 2016). Additionally, self-control is acquired over many years of development, and is critical to academic, social and emotional success. Executive functions and time perception share a common neuroanatomical basis in early development (Neufang et al., 2008). Brain regions associated with self-control are immature at birth and mature gradually during childhood and adolescence (Tarullo, Obradovic, Gunnar, 2009). There is growing evidence from developmental psychology that experience based motor knowledge shapes the development of social cognitive skills and that the development of motor expertise coincides with the emergence of advanced linguistic competence (Gallese et al., 2009). Additionally, the motor cortex plays a crucial role in complex cognitive abilities and forms part of the neural circuitry that accounts for action and intentions, providing a foundation upon which social abilities can be built (Gallese et al., 2009). Furthermore, there is neuroanatomical evidence from evolutionary research suggesting the human cerebellar cortex, along with the dentate nucleus, has dramatically increased in size and reciprocal connections (Barton, 2012; Koziol et al., 2012). A development not found in other species (Koziol et al., 2012). Additionally, the evidence for the cerebral role in a variety of processes including language, affective behavioural modulation and executive functioning and attention is compelling (Barton, 2012; Koziol et al., 2012).

1.7 Timing models

The production and discrimination of temporal patterns at millisecond level is critical to sensory motor processing (Goel & Buonomano, 2014). With regards to theories on how the brain tells time roughly two approaches have been proposed; Intrinsic timing models, relying on local and generalised properties of neural networks, or dedicated timing models, relying on specialised or centralised timing mechanisms (Buonomano

& Laje, 2011; Goel & Buonomano, 2014). There is however still little direct evidence in favour of one or the other approach (Buonomano & Laje, 2011). Only a few biologically realistic neuron based models have been proposed (Buonomano & Laje, 2011) which have the shared assumption the ability of the brain to tell time is proposed to rely on a number of potential mechanisms covering a broad range of different neural substrates (Goel & Buonomano, 2014). The different models vary dramatically in the level of detail broadly speaking four classes of timing models can be categorised: (i) Spectral/delay line models. Spectral models broadly assume that the property of neuron is set to different values allowing each unit to respond selectively to different intervals. Delay line models are similar in that neurons have the ability to buffer the representation of recent events. (ii) Ramping models propose that timing abilities are encoded in the firing rates of neurons. (iii) Oscillator models are based on an array of neural elements which oscillate at different frequencies. (iv) State-dependent network models assume that the dynamically changing active state of neural networks encode time (for reviews please see Buonomano & Laje, 2011 and Goel & Buonomano, 2014).

1.8 Measuring the link between cognitive deficits through motor timing

Modern clinical neuroscience often ignores that the brain functions as a whole and as such views behaviours as separate domains in a typically 'top-down' fashion empathising cortical structures whilst largely ignoring subcortical substructures (Koziol et al., 2012). Contrary to other sensory experiences, timing is challenging to measure in that it has no specific sensory organ- such as touch or sight. However, there is a growing body of research that suggest that cognitive and sensorimotor mechanisms are connected. Experimental motor timing paradigms addressing the

possible link between cognition and movement have been developed (Delevoeye-Turrell et al., 2007, 2012; Dione, Delevoeye-turrell, Wing, Bartolo, & Elliott, 2013).

Recent research indicates that our actions and the interpretation of these actions (our intentions) are implicitly connected through implicit interpretations of our movement and reaction times (Lewkowicz, Quesque, Coello, & Delevoeye-Turrell, 2015). Participants were presented with short video fragments of an individual grasping an object to either use it themselves, or to give it to a partner to use it. Self-reported social cognition, motor imagery and visual imagery was used to measure ability to correctly classify social intention trials through simple observation. Results revealed that the ability to distinguish 'social' from 'personal' actions was predicted by the social skill abilities. A second experiment, conducted by the same researchers, assessed the possible predictive mechanisms contributing to this ability. Results showed that the detection of social intention relies on the variation of both reaction and movement time variabilities implicitly perceived in the grasping action. The authors argue that the ability to use these motor deviants for action-outcome understanding could be the link to human 'intuitive' social interactions (Lewkowicz et al., 2015).

Further research by (Delevoeye-Turrell et al., 2007) comparing and contrasting motor planning abilities of a group of individuals suffering from Schizophrenia (n=24) with a group of healthy controls (n=24) using three motor tasks. Where the first task involved triggered sequences in which sensory information of one movement was the cue for initiation of the following movement the second and third task tested the preplanning ability of action of the participants. Results showed that not only did the group with schizophrenia execute the sequences less fluent than healthy controls, this fluency deficit increased with sequence complexity. In other words, the more

planning was necessary the poorer the performance was. The researchers showed that participants with schizophrenia had higher order motor fluency deficits (planned action) compared to healthy controls (Delevoye-Turrell et al., 2007).

A study comparing sensory motor synchronisation abilities between individuals with schizophrenia, individuals at high risk of developing schizophrenia, and healthy controls (n=39) showed that synchronisation abilities between individuals at high risk of developing schizophrenia and individuals with schizophrenia showed more similarities than comparisons with healthy controls. Motor timing variability revealed that deficits could be detected in the central mechanism involved in the production of rhythmic sequences as early as the prodromal phase of schizophrenia (Delevoye-Turrell et al., 2012). Additionally, spontaneous tapping tempo was positively correlated with cognitive speed in patients, which suggests a central origin for the deficit. Finally, individuals at high risk of developing schizophrenia were characterised by more variable rhythmic patterns, levels which were comparable to that to that observed in the individuals with schizophrenia.

In sum, the generation of human actions represent a complex interaction of cognitive, visual and proprioceptive information: in order to act we need to select the effector, conduct an action, whilst simultaneously determining the target for that action. We plan in order to reach goals, and our perception guides us with regards to the proximity of reaching these goals (Haggard et al., 2002). Actions unfold over time and through a complex sequence of internal events (Yarrow & Obhi, 2014).

Van Hoof (2002; 2003) presents an explanatory model which proposes that psychiatric disorders such as SUDs are underpinned by a dysregulation in dual pathway circuitry which links cognition and sensorimotor processing. These deficits

are caused by developmental and evolutionary factors. Several fields of research suggest that sensorimotor and cognitive mechanisms are connected (Barton, 2012; Lewkowicz et al., 2015). Also the role of the cerebellum in human cognition seems to have been underestimated in modern neuroscientific research (Koziol et al., 2012).

Recent research has demonstrated impairments in motor timing in SUDs (Wittmann, Leland, Churan, & Paulus, 2007), indicating that there may be support for the link between movement and cognition, as proposed by van Hoof (2002, 2003), and that assessment of motor timing could be a valuable prognostic tool in SUDs. Motor timing research, linking cognition and timing abilities used in schizophrenia research, suggests that simple motor tasks may provide a sensitive tool for the detection of pathology and cognitive performance when psychopathology is present (Delevoeye-Turrell et al., 2007, 2012; Giersch, Wilquin, Capa, & Delevoeye-Turrell, 2013; Wilquin & Delevoeye-Turrell, 2012).

The role of movement and timing is shown to play a role in cognition and psychopathology. Besides the link between cognition, motor timing and Schizophrenia, recent research suggests that this link may exist in SUDs (Wittmann et al., 2007). As such simple motor timing tasks may provide a prognostic tool in SUDs. This has not been systematically investigated. The main question of this study was: *Do imbalances between the DM and GM- expressed in motor timing deficits differentiate individuals with SUD from normal controls and predict poorer treatment response and relapse?*

1.9 Study Rationale

Imbalances in the DM and GM are hypothesised to underlie psychiatric disorders such as schizophrenia and SUD. Attention, Impulsivity and Working Memory (WM) are common deficits found in SUD (Goldstein & Volkow, 2002; Stevens et al., 2014, Verdejo-Gargia,

Lawrence & Clark, 2008) and have been shown to be predictors of poor treatment outcome and relapse in Alcohol and Cocaine Use Disorder (AUD and CUD respectively) (Aharonovich et al., 2006; Aharonovich, Nunes, & Hasin, 2003; Bates, Buckman, & Nguyen, 2013; Stevens et al., 2014; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). Previous research using motor timing tasks has shown motor planning, spontaneous movement variability, and synchronisation variability in populations with Schizophrenia compared to HC (Delevoeye-Turrell, Giersch, Wing, & Danion, 2007; Delevoeye-Turrell, Vienne, & Coello, 2011). Based on this, we formulated a research hypothesis to indirectly test the model of van Hoof (2002; 2003) regarding dual circuitry imbalances in SUD populations. Furthermore, motor timing deficits have been found in SUDs (Cheng, MacDonald, Meck, 2006; Wittmann, Leland & Paulus, 2007). However, to our knowledge, this has not been investigated with regards to treatment outcome and relapse. If motor timing shows to be a predictor of treatment outcome and relapse, early screening using simple motor tasks could potentially provide a more sensitive and robust measurement tool of cognitive impairment compared to neuropsychological tests available to us at present. The use of specific motor tasks has shown to be a sensitive measurement of deficits in motor timing in patients with schizophrenia and healthy populations (Delevoeye-Turrell, Giersch, Wing, & Danion, 2007; Delevoeye-Turrell, Wilquin, & Giersch, 2012; Dione, Ott, & Delevoeye-turrell, 2005; Dione, Delevoeye-turrell, Wing, Bartolo, & Elliott, 2013; Dione & Delevoeye-Turrell, 2015). This may allow for early identification of treatment response and relapse in this population.

1.10 Objectives

1.10.1 Primary Objectives

The main objectives of this prospective study were to assess the predictive properties of motor timing with regards to treatment outcome (8 weeks) and risk of relapse at 12 months (yes/no). We further explored possible imbalances between the DM and GM in individuals

suffering from AUD and/or CUD. More specifically, AUD and/or CUD individuals were expected to have a comparatively (with Healthy Controls, HC) high activity of the DM and a comparatively low activity of the GM. Additionally, we compared motor timing differences between individuals with SUD and HC. These differences were compared between SUD individuals and HC and then, within the SUD group, between individuals with AUD and/or CUD.

1.10.2 Secondary Objectives

Secondary objective of this study was to examine whether motor timing improved with prolonged abstinence. Additionally, we assessed the test retest variability of the motor timing task battery. Finally, we examined if motor timing in SUD populations was related to levels of impulsivity, or could be predicted by attention and WM performance

1.11 Aims and Hypotheses

1.11.1 Primary Aims

1.11.1.1 Prognostic value of motor timing in treatment outcomes and relapse

The main aim was to test the theoretical basis for prognostic indicators in SUD with regards to motor timing (measured in terms of treatment response and relapse). We expected i) motor coordination and planning abilities (Motor reaction task [Task 1]; ii) synchronisation abilities (Spatial-tapping task [Task 2]); iii) and decision making (Go-nogo task [Task 3]); would be prognostic of treatment outcomes (self-perceived efficacy to abstain from substances) at 8 weeks and relapse at 12 months (yes/no).

1.11.1.2 A bimodal distribution and evolutionary neurobiological model

Further, we investigated motor timing deficits in SUD populations compared to a HC to indirectly test the model proposed by Van Hoof (2002, 2003). Deficits in motor timing could reflect an imbalance between the DM and GM (i.e., comparatively high activity of the DM and

a comparatively low activity of the GM). We assessed for motor planning and coordination, decision making and synchronisation abilities. We expected decision making to be expressed as the measurable attempt to inhibit making error, or adapting after an error has been made. This would be expressed as faster reaction times after a Go Target compared to reaction times after a Nogo Target and a Nogo Target Error, indicating cognitive control over behaviour. With regards to the DM, we expected to find (i) higher internal clock rate (higher spontaneous rhythms on the Spatial-tapping task [Task 2]); (ii) lower motor coordination and planning (higher reaction times and lower movement times on the Motor reactivity task [Task 1]) and; (iii) lower inhibitory capacities (higher reaction times on the Go stimuli in the Nogo trail and more errors on the Nogo stimuli in the Nogo trail [Task 3]) in SUD individuals compared to HC. With regards to the GM, we expected to find lower synchronisation abilities (the spatial-tapping task trails that are at higher tempi [Task 2]) in addicted individuals compared to HC. Furthermore, we expected that within the SUD group we would find (i) a comparatively lower inhibitory capacity in the cocaine group compared to the alcohol groups (Go-nogo [Task 3]); (ii) the alcohol group would be more sensitive to negative feedback and as a result, a decrease in performance was expected as a result of errors on a speed performance tasks (Go-nogo Error [Task 3]).

1.11.2 Secondary aims

1.11.2.1 Motor timing outcome differences between patients

The aim was to assess recovery in motor timing abilities and individual differences between AUD and/or CUD groups. Specifically, we compared timed motor coordination and planning (Motor reaction task [Task1]), decision making (Go-nogo Task [Task3]) and synchronisation abilities (Spatial-tapping task [Task2]), at baseline, and discharge (week 1 and 8), in three groups (a group with AUD, a group with CUD, and a group with both AUD and CUD). We hypothesized that at 8 weeks, motor coordination and planning abilities (Motor reaction task [Task 1]) would improve at post-treatment for all patient groups as evidenced by:

(i) shorter movement times at increased environmental difficulties (recovery of timed motor coordination/planning abilities, condition 2 & 3 on the Motor reaction task [1]); and (ii) increased decision making abilities (slower reaction times after a Nogo target and after a Nogo error target on the Go-nogo task [task 3]). Lastly, we expected improvement in all patient groups in synchronisation abilities through; (i) lower synchronisation errors and (ii) inter response interval errors, (iii) lower contact times and, (iv) lower spatial error rates [Spatial-tapping task 2]).

1.11.2.2 Test-retest reliability

We examined test-retest variability of the motor task battery comparing the HC motor task performance data at week 1 with data at 8 weeks.

1.11.2.3 Motor Timing, Attention, Working Memory and Impulsivity

We tested whether motor timing in SUD populations was related to levels of impulsivity, and could be predicted by attention and WM performance. With regard to Attention, WM and Impulsivity, we expected to find that (i) motor timing would correlate with measures of impulsivity (higher impulsivity reflecting higher degree of timing deficits) and, ii) that motor timing would not be better predicted by attention and WM deficits.

1.12 Research Design, Methods and Sample

This was a prospective study to test for imbalances between the DM and GM and their prognostic value in patients abstinent of substances (subtypes: alcohol and/or cocaine) attending a rehabilitation programme. Patients were tested at three points in time i) within 72 hours of the start of the intervention, ii) after completion of the intervention at eight weeks (measure of treatment response), and iii) at twelve months' follow-up period (measure of relapse). Participants completed two visits per assessment i) a diagnostic, behavioural assessment, and ii) a neuropsychological and motor timing task assessment. The sample size

was calculated based on the outcomes of a pilot study (see test-retest results in Chapter 3). After the pilot study was completed we decided to shorten the Spatial-tapping Task, by leaving out condition 3 (for a detailed overview of this part of the task please refer to the published protocol in chapter 2, section 2.8.6.2). Reason for omitting this part of the task was that the length of the task lead to patients complained of fatigue. Please note that omitting this part of the task did not affect our overall ability to address the hypotheses. We removed this condition from the protocol. The remaining work does not contain any reference to this particular part of the task.

1.13 Ethical Considerations

This study was performed in accordance with the Declaration of Helsinki (Helsinki, 2001). Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Stellenbosch University. With regards to the healthy controls who were Dutch nationals, ethical clearance was obtained from the University of Amsterdam, the Netherlands. Written consent to conduct research was obtained from Momentum Mental Healthcare, South Africa. Participants recruited in South Africa only received compensation for participation (in the form of a book) upon completion of all study visits. The Dutch control group recruited in the Netherlands was reimbursed with an hourly rate of 10- Euro (which is standard procedure in the Netherlands). Refusal to participate or premature withdrawal from the study did not impact on or prejudice care that patients received.

Patients with alcohol and cocaine dependence continued to receive treatment as planned, either as outpatients or inpatients. The anonymity of patients in the study was ensured through the use of numbered codes. A code, date and time was documented for each participant. All study data and documents were stored on a computer that is password-protected, accessible only to those directly associated with the research. Paper and pen tasks and questionnaires were assigned with participant codes and locked in a filing cabinet. The burden for the patient comprised a clinical interview (30 minutes), neuropsychological testing

(45 minutes) and experimental testing (45 minutes). The risk level was minimal as only non-invasive methods of investigation were used. All assessments were conducted in a structured manner by either the PI, or a trained research assistant. One research assistant was appointed for a period of 2 years. All questionnaire and task performance scores, including data entry, were cross checked by both the PI and the research assistant. All questionnaires and tasks were scored using the official manuals. For the assessments, standard Operating Procedures (SOPs) were followed during all assessments. Task instructions were read out the same way to each participant (for the SOPs and instructions that were read out for the neuropsychological testing, see appendix A; for Motor task testing, see appendix B). The same order of assessment was used for each visit and for each participant.

1.14 Chapter overview

Chapter 1 provides a brief synopsis of the study background, a brief introduction to the model of van Hoof followed by the research areas of major influence on this model. Following on this, ethical considerations and methods, including the main research question, study rationale, and objectives and hypotheses will be discussed.

The following chapters present a comprehensive account of findings related to the specific aims and objectives of this study. These chapters are presented in journal paper format since some of these chapters are in the process of being submitted, have been submitted or have been published.

Chapter 2 presents the PhD study protocol. The protocol has been presented in the format of a recent publication (Young, Delevoye-Turrell, van Hoof, Goudriaan, & Seedat, 2016).

Chapter 3 presents the motor timing performances of the Healthy Control group and Impulsivity and the test retest variability data for the motor task battery. The latter was a

secondary aim of the study. This work is presented in the format of a publication and will be submitted to the Journal *Cognitive Processing*.

Chapter 4 presents the findings from the primary aims of this study. The paper aims to assess motor timing performances in light of clinical outcomes (defined as Self Perceived Self Efficacy to Abstain from Substance Use [Alcohol and/or Cocaine]). They are presented here in the format of a publication and submitted to the Journal of Studies on Alcohol and Drugs

Chapter 5 presents the findings pertaining to the primary aims of this study. The paper assessed for differences in motor timing performances in Cocaine and/or Alcohol groups at baseline and at discharge, examining for possible recovery of motor timing (visit 1 and 2). The chapter has been presented here in the format of a journal article, as this section will be submitted for publication.

Chapter 6 presents the findings from the primary aims of this study. The paper compared Patients and Healthy Controls and Cocaine and/or Alcohol groups on motor timing abilities. The outcomes are discussed with reference to the van Hoof model (e.g. the drive and guidance mechanisms deficits). The chapter is presented here in the format of a manuscript and will be submitted for publication with *Special series of BMC 'Evolutionary Biology'*.

Chapter 7 presents the findings from the secondary aims of this study. The study aimed to assess the patient data as a whole. Motor timing performances were correlated with regard to impulsivity. Regression analyses were used to assess the effects of working memory and attention with regard to motor timing. The chapter is presented here in the format of a manuscript, as this section will be submitted for publication.

Chapter 8 presents the conclusions and direction for future research

1.15 References

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Young, S. Y., Delevoye-Turrell, Y., van Hoof, J. J. J., Goudriaan, A. E., & Seedat, S. (2016). Association between motor timing and treatment outcomes in patients with alcohol and/or cocaine use disorder in a rehabilitation program. *BMC Psychiatry*, 16(1), 273. <https://doi.org/10.1186/s12888-016-0968-5>

2 Association Between Motor Timing and Treatment Outcomes in Patients with Alcohol- and/or Cocaine Use Dependence in a Rehabilitation Program

Chapter 2 presents the PhD research protocol. Please note that the authors' contributions have been noted in the article. The protocol has been presented here in the format of the following protocol publication:

Publication: Young, S. Y., Delevoeye-Turrell, Y., van Hoof, J. J. J., Goudriaan, A. E., Seedat, S.(2016). Association between motor timing and treatment outcomes in patients with alcohol and/or cocaine use disorder in a rehabilitation program. *BMC Psychiatry*, 16(1), 273. <http://doi.org/10.1186/s12888-016-0968-5>

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2.1 Abstract

Introduction Individuals with Substance Use Disorders (SUDs) are found to have disruptions in the brain's dopaminergic (DA) system and the functioning of its target neural substrates (striatum and prefrontal cortex). These substrates are important for the normal processing of reward, cognitive control and motivation. Cognitive deficits in attention, impulsivity and working memory have been found in individuals with SUDs and are predictors of poor SUD treatment outcomes and relapse, in alcohol and cocaine dependence specifically. Furthermore, the DA system and accompanying neural substrates play a key role in the timing of motor acts (motor timing). Motor timing deficits have been found in DA system related disorders and more recently also in individuals with SUDs. Motor timing is found to correlate with attention, impulsivity and working memory deficits. To our knowledge motor timing, with regards to treatment outcome and relapse, has not been investigated in populations with SUDs. **Methods** This study aims to investigate motor timing and its relation to treatment response (at eight weeks) and relapse (at twelve months) in cocaine and/or alcohol dependent individuals. The tested sensitivity values of motor timing parameters will be compared to a battery of neurocognitive tests, owing to the novelty of the motor task battery, the confounding effects of attention and working memory on motor timing paradigms, and high impulsivity levels found in individuals with SUDs. **Discussion** This research will contribute to current knowledge of neuropsychological deficits associated with treatment response in SUDs.

2.2 Keywords

Motor Timing, Impulsivity, Addiction, Substance Dependence, prognostic value, Biomarkers, Action Planning, Executive Functioning, Attention, Working Memory, Theoretical frameworks for Substance Use Dependence.

2.3 Background

Although etiological models of substance use disorders (SUDs) differ from one another at the level of neurobiological and social cognitive explanations, the overall picture is that there are at least two semi-dependent behavioral systems in the brain involved: (i) a fast associative impulsive system and (ii) a slower reflective system. Both of these systems are susceptible to change through substance use (alcohol & cocaine) (Van Hoof, 2002; Volkow, Wang, Fowler, & Telang, 2008). Substance dependence and the specific lack of behavioral autonomy associated with substance intake is primarily guided by direct reward, high impulsivity, difficulty in foreseeing the consequences of actions, and difficulties in planning behavior (Bechara, 2005; Goldstein et al., 2009; Goldstein & Volkow, 2011; Kalivas, Volkow, & Seamans, 2005; Koob & Le Moal, 2005; Leeman & Potenza, 2012). Research suggests that difficulties in delaying gratification, impulsivity and inhibition may be caused by temporal processing deficits (Arce & Santisteban, 2006; Wittmann & Paulus, 2008). The dopaminergic system and its target neural substrates (striatum and prefrontal cortex), which neuro-anatomically and neuro-physiologically underpin SUDs (Goldstein et al., 2009; Kalivas et al., 2005; Volkow et al., 2004), are important neural systems for the timing of motor acts (Pine, Shiner, Seymour, & Dolan, 2010; Wittmann et al., 2007).

2.4 Motor timing, cognitive deficits and SUD

Timing is crucial when individual outcomes are considered and decisions are made (Wittmann & Paulus, 2008). A recent review of the literature on time perception, impulsivity and decision making found that impulsive individuals perceive time differently (Arce & Santisteban, 2006;

Wittmann & Paulus, 2008). Time is perceived at a higher cost, leading to overestimation of the duration of time intervals and consequently discounting the value of delayed rewards more strongly than low-impulsive individuals. Additionally, an increased state of arousal, possibly driven by emotional distress, is arguably the main factor that alters the way in which impulsive individuals take time into account when making decisions [for a detailed review please see 10]. A recent review of the literature on impulsivity concluded that many tasks confound timing abilities (e.g., motor impulsivity, time estimation deficiencies, and reward discrimination features). These factors are all known to cause an individual to act impulsively (Arce & Santisteban, 2006) and the question that arises is whether timing should be considered as a contributory cause of impulsive behaviour (Pine et al., 2010). As such, it may be necessary to consider timing confounds in new research paradigms since timing deficits could be a precipitating factor for impulsivity (Arce & Santisteban, 2006).

Whereas existing theories of the effects of DA highlight its crucial role in reward learning and disinhibition, they do not offer an account of the pathological hypersensitivity to temporal delay which is one of the phenotypes of SUDs (Pine et al., 2010). This hypersensitivity has been examined. Timing aspects of impulsivity were tested through either pharmacological enhancement of dopamine or placebo using an intertemporal choice task and functional magnetic resonance scanning. The results showed that by explicitly probing the relationship between the utility of rewards and their timing, independently of feedback and learning, DA increased impulsivity by enhancing the diminutive influence of increasing delay on reward value and its corresponding neural representation in the striatum (Pine et al., 2010). These findings reveal a novel mechanism by which DA influences human decision making by controlling the relationship between the timing of future rewards and their subjective value. DA, therefore, selectively impacts the discounting of future rewards (time till reward is received) and it does this without any significant effect on the value of the utility of this reward (Pine et al., 2010).

There are no neurological disorders that are characterized by temporal deficits (Jennifer T Coull, Cheng, & Meck, 2011). It is thus difficult to tease apart if the observed temporal processing deficits in actual fact reflect increased sustained attention or working memory demands (which are required by timing tasks). Thus timing deficits may actually reflect cognitive deficits (Jennifer T Coull et al., 2011) and vice versa. Deficits in attention and working memory are thought to impair the ability to plan ahead and consider all information available before choices are made without considering all alternatives (Arce & Santisteban, 2006). Individuals with SUDs show deficits in attention and working memory (Wittmann et al., 2007). Timing deficits have been associated with attention and working memory. A number of human timing studies have indicated that sustained attention and working memory are crucial in accurate estimations of intervals in the seconds range (Wittmann et al., 2007). Further, the inability to retain several alternatives to be evaluated in memory or the inability to foresee the future all lead to increased impulsivity (Arce & Santisteban, 2006). One of the few studies to date that attempted to examine motor timing in stimulant dependent individuals, whilst controlling for possible confounds, found that motor timing deficits are present in this population (Wittmann et al., 2007). The stimulus dependent group showed abnormal motor timing abilities on all timing tasks, except sensorimotor synchronisation. With regard to neuropsychological deficits other than timing, only the overestimation of a relatively long time interval could be explained by impulsivity. These results indicate that stimulant dependent individuals exhibit motor timing deficits that cannot be explained by cognitive deficits (Wittmann et al., 2007).

2.5 Evolutionary and developmental perspectives on SUDs

In line with the literature on dual circuitry deficits in SUD (Volkow et al., 2008), van Hoof has argued that SUDs can be explained through evolutionary and developmental processes. SUDs result from an imbalance between a stimulus-driven mode of action (Drive Mechanism) and a more cognitive-predictive mode of action (Guidance Mechanism). At the core of van

Hoof's model (van Hoof, 2003; Van Hoof, 2002), is the hypothesis that during phylogenesis, as during ontogenesis, these two distinguishable mechanisms, relevant for grasping stationary respectively moving objects, are implemented in a repetitive way from the motoric area into the limbic area of the brain, resulting in the capacity to organize intentional behaviour. Individual personality differences shape the development of both of these mechanisms in an innate bimodal distribution (e.g., manifesting as personality traits such as extroversion or introversion). Extroverts show a bimodal distribution of personality traits; sensitive for punishment (negative feedback) resulting in avoiding neurotics, or insensitive for punishment (negative feedback), resulting in blunted antisocial or narcissistic personality traits.

The Drive Mechanism, a feedback mechanism, is hypothesized to be effected and implemented through a ventral circuitry that runs through the orbitofrontal cortex which includes the parietal cortex, the ventral premotor cortex and the basal ganglia. The Drive Mechanism is based upon a compilation of stimulus–response rules specifying the motor routines that objects habitually require (sensorimotor learning). The Guidance Mechanism, a dorsally located feed-forward control mechanism, runs through the dorsolateral prefrontal cortex. This is a more cognitive–predictive mode of action based on a compilation of action–effect rules specifying the actions and the effects produced in the future and is mediated by fronto–striatal circuits. For this mechanism to work properly the timing of motor movements is crucial (van Hoof, 2003; Van Hoof, 2002). Both circuitries circumnavigate the same anatomical structures, namely the cortex, striatum, globus pallidus and thalamus (van Hoof, 2003; Van Hoof, 2002).

This bimodal distribution and evolutionary neurobiological model may provide a useful pathogenic framework for the classification of major psychiatric disorders, including SUDs (van Hoof, 2003; Van Hoof, 2002). Indeed, most psychiatric disorders are believed to be defined by some level of dysfunction in ventral and/or dorsal systems and there is a body of literature to support this (Comte et al., 2014; Herwig, Prinz, & Waszak, 2007; Hommel, 2003; Kalivas et al., 2005; Logan & Cowan, 1984; Prinz, 1997).

1.5 Rationale

Attention, impulsivity and working memory deficits are commonly found in SUDs (Goldstein & Volkow, 2011; Stevens et al., 2014; Antonio Verdejo-García, Lawrence, & Clark, 2008; Wittmann & Paulus, 2008) and are predictors of poor SUD treatment outcomes and relapse in alcohol and cocaine dependence specifically (Aharonovich et al., 2006, 2003; Stevens et al., 2014; Turner et al., 2009). These deficits are in line with van Hoof's (2003) model of imbalances in Drive and Guidance Mechanisms (a stronger Drive relative to the Guidance mechanism). According to van Hoof, the ability to time actions is crucial factor for a well-functioning Guidance mechanism. Motor timing deficits correlate with attention, working memory deficits and impulsivity (Jennifer T Coull et al., 2011; Ivry & Spencer, 2004) and have been found in individuals with SUDs (Wittmann et al., 2007). To our knowledge, these timing deficits have not been investigated with regard to treatment outcome and relapse in SUDs. Early detection of motor timing deficits may be predictive of treatment outcome and relapse risk. Cognitive training of motor timing as well as alternative activities that function as distractors to inhibit premature responses may be potentially useful interventions.

2.6 Study Aims

This is a prospective, ongoing, study which aims to examine the prognostic value of motor timing deficits in SUDs. These deficits are thought to reflect deficits in the Drive Mechanism and Guidance Mechanisms. We hypothesize that motor timing pre-treatment will be correlated with treatment response and relapse rates after treatment (which forms part of the standard care at the participating centre). Second, we will assess whether different subtypes of substance dependence (alcohol and/or cocaine) can be distinguished by task performance on a variety of tasks. We will compare task performance in patients with SUDs and healthy controls (HC) at pre- and post- completion of the treatment programme to avoid possible test-retest confounds. Third, we will test if motor timing performances correlate with impulsivity and attention and working memory functions. Fourth, we aim to find support for the model of van

Hoof (van Hoof, 2003; Van Hoof, 2002).

Three contrasting motor tasks will be used. All patients will be pair-matched with healthy controls for age, sex and ethnicity. The tested sensitivity values of the motor timing parameters will be compared to a carefully selected battery of neurocognitive tests. This is necessary due to the novelty of the motor task battery, the confounding effects of attention and working memory on motor timing paradigms (Jennifer T Coull et al., 2011), and the high impulsivity levels found in SUDs (Stevens et al., 2014). This study does not only have the potential to make a valuable contribution to both the SUD and motor timing literature but could further provide knowledge of the mechanisms at play in SUDs. If motor timing has prognostic value in the treatment of SUDs, simple motor timing measures can be incorporated in the management of patients and in the monitoring of outcomes.

2.7 Hypotheses

This prospective study will test the theoretical basis for prognostic indicators in SUD and its subtypes with regards to motor timing (measured in terms of treatment response and relapse). We hypothesise to find deficits in motor timing in SUD patients (alcohol and/or cocaine) compared with age-, gender-, and education-, ethnicity- and handedness- matched HC. We expect to find; i) a higher internal clock rate (higher spontaneous rhythms on condition 2 of the Spatial-tapping task [Task 2]); ii) a lower capacity to structure, organise and plan an action directly towards a visual target (higher reaction times and lower movement times on the Motor reaction task [Task 1]); ii), lower inhibitory capacities (higher reaction times on the Go stimuli in the Nogo trail, more errors on the Nogo stimuli in the Nogo trail, and lower cognitive flexibility Go-nogo task [Task 3]) in addicted individuals compared to HC. With regards to van Hoof's model we expect to find; iii) a comparatively high activity of the Drive Mechanism and a comparatively low activity of the Guidance Mechanism. High activity in the Drive Mechanism will be reflected by hypotheses i and ii. We expect to find that the above hypotheses will; iv) correlate with lower treatment response and higher relapse in addicted patients (alcohol and/or

cocaine), v) that timing deficits will correlate with measures of impulsivity (higher impulsivity reflecting higher degree of timing deficits) and, vii) that timing deficits will not be better explained by attention and working memory deficits.

2.8 Methods

2.8.1 Sample

The study sample will consist of a group of 75 abstinent patients diagnosed with alcohol and/or cocaine dependence and a group of 35 healthy controls (HC). The sample size has been calculated based on the outcomes of a pilot study (a detailed report of the sample size calculation can be found in the Data Analysis section below). The pilot study consisted of 20 Addicted individuals (Cocaine and Alcohol) and 20 matched HC. For the study, four groups of participants, aged between 18 and 55, will be recruited: cocaine dependence only, alcohol dependence only, both cocaine and alcohol dependence, and a group of matched healthy controls. All diagnostic tools and assessments will be administered in either English or Dutch (the majority of the patient admitted to the clinic are Dutch nationals). Qualitative and quantitative information on the use of nicotine, caffeine and other psychoactive substances will be obtained through detailed questionnaires covering past and current use, as these substances are potential confounders and may contribute to performance modulation on experimental tasks (Rzepecki-Smith et al., 2010).

2.8.2 Inclusion/exclusion criteria

Patients with a primary diagnosis of alcohol or cocaine dependence, or both, who have been detoxified, who are willing to provide written informed consent, and who can speak English (minimum 6th grade level) will be included. Urine toxicology screening will be conducted in all participants. Patients who meet criteria for dependence for any substance other than cocaine/alcohol will be excluded. Patients who meet criteria for abuse (lifetime or

current) of other substances will be included, provided that these are not primary drugs of use/abuse. Patients will be excluded if they have a neurological disorder; history of hepatic encephalopathy (for participants with alcohol dependence); a history of head trauma; or any current medical illness; neurological disorder (e.g. brain trauma with loss of consciousness); any psychotic disorder or antisocial personality disorder according to the DSM-IV-R (American Psychiatric Association, 2000); mental retardation; or lasting injuries to the hands. For the alcohol group, patients will be excluded if they have a current or past history of dependence on cocaine. For the cocaine group, patients with a current or past history of alcohol dependence will be excluded.

2.8.3 Procedures

Participants will all be inpatients at a private treatment programme for drug/alcohol dependence at the treatment clinic in Somerset West, South Africa. The clinic offers treatment to individuals mainly of Dutch nationality (main patient referral company is situated in the Netherlands). The clinic offers a comprehensive primary care treatment program which centres on an 8-week cycle and is comprised of group therapies, individual counselling, written work and a psycho-educational lecture series. All participants work with an individual therapist who will guide them through the process. All participants will have been detoxified prior to arrival. Only participants who are 18 years and older and who have provided written informed consent will be included. Participants will receive compensation for their participation in the form of a book on SUD recovery. The treatment program will form part of the standard of care for all participants. Participants will be tested at three points in time: (i) within 72 hours of the start of the treatment programme, (ii) after completion of the treatment programme at eight weeks (measure of treatment response), and (iii) at 12-month follow-up (measure of relapse). A full medical examination will be conducted on every patient at the clinic (toxicology + biochemistry reports and physical examination by the resident medical doctor). Designated counsellors at the clinic will enquire from patients about their potential interest in study participation. Only participants who give written consent and who are eligible on screening will

be invited for a first research visit. After written consent is obtained the Measurements in the Addictions for Triage and Evaluation.2 (MATE.2.10) (Schippers, Broekman, Buchholz, Koeter, & Van Den Brink, 2010), a semi-structured diagnostic interview (MINI) (Lecrubier, Sheehan, Weiller, Amorim, Bonora, Sheehan & Janavs, 1997), and a socio-demographic questionnaire will be administered.

Two study visits will be conducted at the clinic. Each of these visits will entail filling out self-report questionnaires, neuropsychological testing and experimental motor task testing. All assessments will be conducted by the principal investigator or a trained research assistant. After completion of the first visit an appointment for a second assessment will be made. Both assessments will be undertaken within 72 hours of initiation of the treatment program and will be repeated at the end of the eight week (last 72 hours). A telephonic interview using the MATE.2.10 (Schippers et al., 2010) will be used as the follow-up procedure at twelve months as a measure of relapse. To avoid test-retest confounding effects, HCs will be assessed in parallel to the clinical groups. The HC group will be recruited in the Netherlands and assessed and reassessed at eight weeks, identical to the patient groups.

2.8.4 Measures

Gender, age, handedness, ethnicity, education, family history of substance dependence, previous admissions/counselling/therapy history, symptoms of disability, and drug or alcohol usage (including last intoxication, last drink and last withdrawal), depression, impulsivity and psychopathology will be assessed with a self-administered demographic questionnaire, the *Edinburgh Handedness Questionnaire* (EHQ) (Büsch, Hagemann, & Bender, 2010), The MATE.2.10 (Schippers et al., 2010), Mini International Neuropsychiatric Interview version 5 (MINI 5) (Lecrubier et al., 1997), The *Alcohol Use Disorders Identification Test* (AUDIT) (Lundin, Hallgren, Balliu, & Forsell, 2015), and *Drug Use Disorders Identification Test* (DUDIT), (Hildebrand, 2015) *Sheehan Disability Scale* (SDS)(Beck et al., 2004) The *Alcohol Abstinence Self-Efficacy Scale* (AASE) AND The *Cocaine Abstinence Self-Efficacy*

Scale (DiClemente, Carbonari, Montgomery, & Hughes, 1994) and the *Beck Depression Inventory* (BDI) (Beck, Steer, & Carbin, 1988). Self-reported impulsivity will be measured with the *Barratt Impulsiveness Scale Version 11 (BIS-11)* (Patton, Stanford, & Barratt, 1995).

2.8.5 Neuropsychological Assessments

Motor timing will be compared and contrasted with executive functions of attention, impulsivity and working memory using the Corsi (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000), the Stroop Colour Word Task (Lezak, n.d.), Trail Making Test (Lezak, 2012), the Stop-Signal Task (Band, van der Molen, & Logan, 2003), the Letter-Number Sequencing Task (LNS, WAIS –III) (Lezak, 2012), and the Iowa Gambling Task (IGT) (Buelow & Suhr, 2009).

2.8.6 Action-Based Timing Tasks

The motor tasks consist of a series of reaction-prediction visuo-motor pointing tasks to measure different aspects of motor timing. The motor task battery consists of three sequential pointing tasks for measuring different aspects of motor timing (motor reactivity; synchronisation; distractibility; and decision-making), designed by Professor Y. Delevoye-Turrell and her team at the University of Lille, France. These tasks have been used in previous research but not in populations with SUDs (Delevoye-Turrell et al., 2007, 2012; Dione et al., 2005; Dione et al., 2013; Dione & Delevoye-Turrell, 2015). For testing, subjects will be seated in front of a tactile screen (Elo Touch) of 43cm by 36cm by 30 cm which is placed close to the subjects' midline in order to avoid muscle fatigue from the repetitive pointing movements. Visual and auditory signals will be controlled via a PC with coded software in C++.

2.8.6.1 [1] Reactivity: Motor reaction task

Motor reactivity (speed of action initiation) was evaluated using a simple finger-pointing task to visual dots presented on the touch screen. Participants are required to point and touch one dot (condition one), a series of two (condition 2) or of 3 dots (condition 3) that are aligned (figure 2.1). The manipulation of the complexity (the number of dots) of the motor sequence provides the means to assess the capacity of participants to structure, organize and plan an action taking place in the immediate future to ensure accurate pointing in combination with fast movements. Participants were instructed to start with their index finger of their dominant hand placed on the square starting zone which is situated at the bottom left edge of the screen. As soon as a black dot appears on the screen, their task is to lift and touch the central target (square) as fast as possible. Three levels of complexity will be counterbalanced: one target; two-target or three-target conditions. In all conditions, we calculated the means and standard deviations of reaction- and movement time for each individual. The reaction time will be measured as the time between target presentation and finger lift off of the square. The movement time will be measured as the time of lift off and touch of first target (in all conditions). Figure 2.1 illustrates task one.



Figure 2-1 Motor reaction task

2.8.6.2 [2] Synchronisation and distractibility: Spatial-tapping task

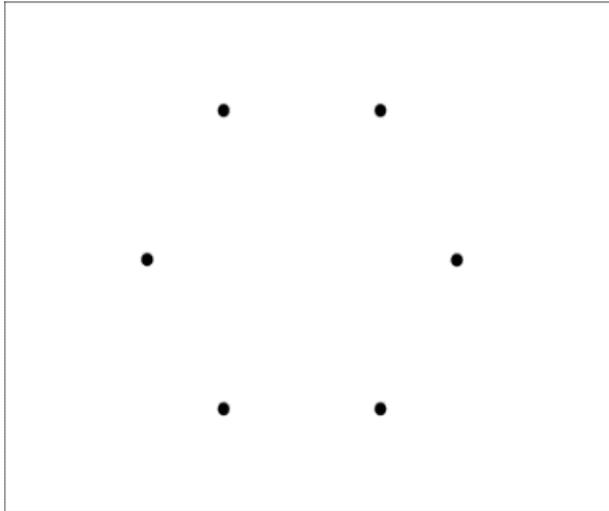
Synchronising movements to external events is an ability that is central to adaptive behaviour. With this task we aim to evaluate how well self-initiated actions to external stimuli, present in the environment, are timed (synchronised) using a Spatial-tapping task (Dione et al., 2013). This task measures pointing accuracy in time and space as well as finger contact duration on the tactile screen. Participants will be seated in front of a tactile screen (Elo Touch) displaying six black dots in a circle of 100 mm apart. The task is to touch each target, one after the other, starting from the bottom right target, and moving counter-clockwise using the right index finger (fist closed). Each condition is constituted of a series of sixty taps, participants perform a total of 5 trials and the total duration of the session is approximately 10 minutes. There are three experimental conditions:

(1) In the spontaneous phase, the task is to point the 6 visual targets at a free and natural pace. This provides the means to evaluate an individual's pacing internal clock but also to evaluate space accuracy in a non-structured environment.

(2) In the rhythmic phase, participants are presented with an auditory rhythm that must be used to pace their actions (ISI= 1100m/sec; 700m/sec, 500m/sec, 400m/sec, and 300m/sec). After listening to the tones for 4.5s, participants start tapping for a total trial duration of 35s. Two blocks of 10 trials are performed.

(3) In the flash phase, participants are presented with random black dots which are flashed across the workspace and are not in rhythm with the auditory rhythm that must be used to pace their actions (the participants ISI from the spontaneous phase is used as the metronome rhythm speed). After listening to the tones for 4.5s, participants start tapping for a total trial duration of 35s. This condition provides the means to test the strength of the representation-based goals for action, i.e. a subjects' capacity to resist distractibility in function of the complexity of the internal representation that they must retain. Figure 2.2 illustrates task two.

Figure 2-2 Spatial-tapping task

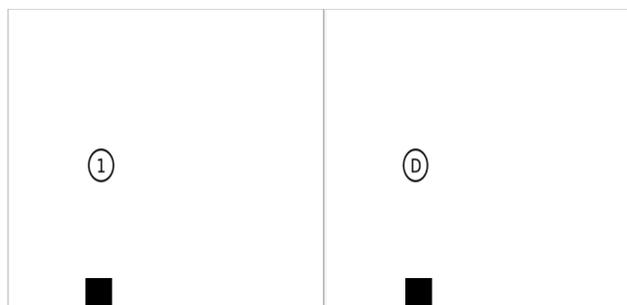


2.8.6.3 [3] Decision-making: Go- nogo task

In order to achieve positive outcomes in the future and function effectively, impulsive urges for immediate gratification have to be postponed and goal directed behaviour has to be given preference (Zimbardo & Boyd, 1999). To do this effectively and efficiently, cognitive control is necessary. Flexible goal-directed behaviour requires an adaptive cognitive control system for selecting contextually relevant information and for organizing and optimizing information processing. For the purpose of this study a modified version of the Go-nogo paradigm will be used. The task aims at the measurement of reaction times through a tactile touch of the touch screen. Starting zone which is situated at the bottom left edge of the screen. The target is a white circle with a black letter or one-digit black number and participants are instructed to act as fast as possible (Go) or to refrain from acting (Nogo) depending in the condition of the task. In a first condition, the task is to tap the target that appears as fast as possible (100% Go). In the following blocks, participants are instructed to react and tap the target as fast as possible only if the target is a letter (50 % Go). If the target is a number, they are to refrain from reacting. Numbers and letters were presented in semi-random order. The

targets were presented for 5s on the screen, with a random phase lag of ± 300 m/sec in order to avoid anticipatory responses.

Figure 2-3 Go-nogo task



2.9 Data Analysis

2.9.1 Power and sample size calculations

The ability to time self-generated movements to an external metronome requires the cognitive functions to speed up or to slow down the planned motor actions. Studies are beginning to show that this ability to modulate the timing of motor sequences requires specific execution functioning (Brown, 1997; Dione & Delevoeye-Turrell, 2015; Ogden, Salominaite, Jones, Fisk, & Montgomery, 2011). Hence, the primary task used in the motor timing battery is a synchronisation task that requires executive control of when to initiate self-generated motor actions.

We have conducted a pilot study in which 20 addicted individuals (cocaine and alcohol) and 20 age-matched healthy controls were tested. From these data, an effect size for the main study was computed on the primary task that is referred to here as the synchronisation task. Power analysis can be used to calculate the minimum sample size required to accept the outcome of a statistical test with a particular level of confidence. Considering the alpha level (0.05), the number of predictors (4 groups), the anticipated effect size required to dissociate pathological patterns of results (0.020 sec), and the desired

statistical power level (0.85), the minimum required sample size in the present study is 24. For testing on the tasks below, we will thus be recruiting 25 patients for each of the three SUD groups and 35 healthy controls in order to control for age and socio-demographic variables as best as possible.

2.9.2 Motor tasks

2.9.3 [1] Reactivity: motor reaction task

Three levels of complexity will be counterbalanced: one target; two-target or three-target condition. In all conditions, we will calculate for each individual the means and standard deviations for reaction time (time between target presentation and finger lift off of the square square) and movement time to the first target only.

2.9.4 [2] Synchronisation task

The two conditions, with and without flashes will be analysed separately.

2.9.4.1 Timing performance

Inter-response intervals (IRIs) will be measured as the time intervals between the start of two successive taps. The IRI error will then be computed as the percentage of absolute difference between each IRI and the reference inter-stimulus interval (ISI) of a given trial and will be used as an indicator of timing (synchronisation) capacity.

2.9.4.2 Spatial performance

The endpoint distributions of the pointing actions will be plotted as a function of each visual target position. Through vector calculations, spatial ellipses will then then calculated. The mean spatial error (SE) of the spatial ellipses will finally be measured in mm² as an indicator of the spatial performance (Dione & Delevoeye-Turrell, 2015).

2.9.4.3 Control of Pauses

The contact time (CT) will be defined as the time of finger contact with the touch screen. This measure (in m/sec) will be used as an indicator of the amount of voluntary pauses in the gesture.

2.9.5 [3] Go- Nogo task

The mean reaction times for the Go trials in the first session will be calculated for each individual. The mean reaction times for the Go trials in the second session will then be calculated as a function of the nature of the preceding trials. More specifically, we will categorise the Go trials as follows (1) a correct Go trial, (2) a correct Nogo trial and (3) an incorrect Nogo trial. Cognitive control will also be evaluated in this task. To do this, the mean reaction time obtained before a Go stimulus will be compared to the mean reaction time obtained before a Nogo stimulus and the mean reaction time obtained before a Nogo error.

2.9.6 Neuropsychological measures

Correlational analyses will be performed between the motor timing parameters and the performance scores obtained on standard neuropsychological tests. A mixed model repeated measures ANOVA will be conducted with three factors included: group, time (pre and post) and group*time (interaction). The group*time interaction is the critical effect to be evaluated because it tests the hypothesis that the change over time (from pre to post), if any, is the same for all groups. Normality assumptions will be checked and suitably addressed if necessary (either through transformation of the response variables or employment of non-parametric techniques like Mann-Whitney U and Wilcoxon matched pairs test).

2.10 Discussion

In sum, impulsivity, deficits in working memory and attention, and motor timing have all been

associated with SUDs. It has been argued that attention and working memory are closely interconnected with impulsivity and motor timing (Jennifer T Coull et al., 2011; Ivry & Spencer, 2004; Radua, Pozo, Gómez, Guillen-Grima, & Ortuño, 2014; L. Stevens et al., 2014; Wittmann et al., 2007). However whether motor timing deficits are due to deficits in attention and working memory is unclear since all three processes are known to engage the right PFC (Jennifer T Coull et al., 2011). Further, impulsivity, deficits in working memory and attention have been established as predictors of both poor SUD treatment outcomes and relapse and are often the focus of cognitive training interventions in SUD and these deficits, at least in part, are amenable to treatment, may recover with targeted treatment (L. Stevens et al., 2014), and may recover spontaneously when the length of abstinence increases. Motor timing deficits have not only received less attention in SUD research, but the prognostic value of motor timing deficits with regards to treatment outcomes and relapse has not yet been investigated. This study will investigate whether timing parameters play a role in executive functions in SUDs. This study will not only extend the motor timing literature, it will also enhance knowledge of the mechanisms that play a central role in SUDs (van Hoof, 2003; Van Hoof, 2002).

2.11 Declarations

2.11.1 Below is a list of Abbreviations used in the study.

SUD	Substance Use Disorder
DA	Dopamine
PFC	Pre Frontal Cortex
EHQ	Edinburgh Handedness Questionnaire,
MATE.2.10	Measurements in the Addictions for Triage and Evaluation.2
MINI	Mini International Neuropsychiatric Interview

AUDIT	Alcohol Use Disorder Identification Test
DUDIT	Drug Use Disorder Identification Test
SDS	Sheehan Disability Scale
AASE	Alcohol Abstinence Self-Efficacy Scale
CASE	Cocaine Abstinence Self-Efficacy Scale
BDI	Beck Depression Inventory
BIS-11	Barratt Impulsiveness Scale Version 11
TMT	Trail Making Test
LNS	Letter- Number Sequencing Task
IGT	Iowa Gambling Task

2.11.2 Ethical Approval and consent to participate

This study will be performed in accordance with the Declaration of Helsinki and the South African Guidelines for Good Clinical Practice. Ethical clearance has been obtained from the University of Stellenbosch's Health Research Ethics Committee (N12/11/080) and the University of Amsterdam (2014-DP-3766). Written consent to conduct this research at Rustenburg Addiction Care/Momentum Mental Healthcare South Africa has been obtained. Participation will be voluntary and will not affect the treatment process. All participants are above 18 and participate freely after signing a written informed consent. The consent procedure entails a very detailed written research information leaflet and a consent form.

The participant will be asked if all research elements are clear and if all questions have been answered before written consent is requested. The voluntary aspect and freedom to withdraw from the study at any time are reinforced. All the tasks proposed in this study are behaviour only and provide no direct medical care to the patients. Indeed, all tests will be

group analyses. The studies are experimental, i.e., the patients' results will be contrasted to those collected in healthy pair matched controls. The studies are non-invasive using motor control tools only, i.e. tactile screens and neuropsychological test batteries. Hence, there is no risk in participating in the experimental sessions. Participants recruited in South Africa will only receive compensation for participation (in the form of an addiction recovery book) upon completion of all study visits. Refusal to participate or premature withdrawal from the study will not impact on or prejudice care that patients are getting or will be getting. The burden for the patient is a clinical interview (1hour), neuropsychological testing (1 hour), experimental testing (1 hour) at the start and end of the eight-week treatment program, and a follow up interview of 20 minutes. If a subject feels fatigued or does not wish to continue with the experiments, he/she can stop immediately. Participants will be free to withdraw from the study at any time without prejudice.

2.11.3 Consent to publish

Not applicable

2.11.4 Availability of data and materials

The dataset that will be collected and analysed for the current study will be available from the corresponding author on reasonable request.

2.11.5 Competing interests

None to declare

2.11.6 Funding

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2.11.7 Author's Contributions

SY Young: Drafting of the manuscript and revising the protocol. Dr JJM van Hoof: Participated in the design of the study and critically revised the manuscript. Professor Y Dellevoeye-Turrell: Designer of the motor tasks battery and participated in the design of the study, planning of data analyses, and critically revised the manuscript. Professor S Seedat: Participated in the design of the study, drafting and revising the protocol. Professor AE Goudriaan: Participated in the design of the study, and critically revised the manuscript. All authors read and approved the final manuscript.

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2.11.9 Author's Information

Prof Soraya Seedat, MBChB, MMed (Psych), FC Psych (SA), PhD is supervising the PhD project of first author Susanne Bakelaar (PhD candidate Psychiatry). Dr Jacques van Hoof, MD, PhD is head of research at Momentum GGZ, Veldhoven (addiction care clinic in the Netherlands) and Momentum Mental Healthcare SA in Somerset West, South Africa and co supervising the project. Professor Y. Delevoeye-Turrell is a co- investigator on the study, developer of the motor task battery used in this study, and, with has special research interests in basic human motor functions (prediction, reaction, adaptation), theory of internal models for motor performance, the sense of agency, and the development of new behavioural tools for use in clinical research. Professor A. Goudriaan, is co-investigator in this study and a professor in mechanisms and treatment in addiction at the Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and at Arkin Mental Health Care, Amsterdam, the Netherlands.

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3 Vulnerability Factors in Motor Timing: Impulsivity in a Non-Pathological Population

Chapter 3 presents the motor timing performances of the Healthy Control group in light of Impulsivity and the test-retest variability of the motor task battery. The latter was a secondary aim of the study. The findings have been presented here in the format of a manuscript, as this section will be submitted to a peer reviewed journal.

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3.1 Abstract

Introduction: Impulsivity has been linked to factors which are negatively correlated with behaviour relevant to health, such as drug and alcohol use, substance abuse, and violence.

Methods: This study examined the association of rapid response impulsivity (RRI) with higher and lower order motor timing deficits and the test-retest variability of a motor timing task battery. Additionally, the study examined the test-retest reliability of the impulsivity test battery

Results: Results of the group comparisons found that non-pathological RRI affects the strategic coordination of temporal processing of voluntary motor behaviour. With regard to interval timing, there were significant differences between the high and low RRI groups. On average, high RRI individuals had a higher error percentage than low RRI individuals, which was statistically significant at fast tempi. The high RRI group was also less able to synchronise sequential movements during interval timing. This difference was significant at slower tempi. Our results show no differences in motor planning and cognitive control using the Go-nogo task between high and low RRI groups. Good test-retest reliability of the Impulsivity test battery was found for all tasks. **Conclusions:** High and low RRI individuals in healthy non-pathological populations differ with regards to motor timing abilities. These differences seem to indicate specific and not general timing deficits. This research provides a valuable contribution to impulsivity research in healthy populations but requires replication in larger samples.

3.2 Background

The accurate timing of our actions is fundamental to our survival as a species (Stevens et al., 2007), since it not only lays the foundation for the coordination of motor sequences and the production of voluntary interactive behaviours, but also aids the structuring of thoughts and sensations (Allman, 2015). However, our actions are governed both by our timed self-controlled and reasoned attitudes and our impulses. Only recently have psychologists come to appreciate that acting and knowing are inseparable. Indeed, purposeful movements, and not responses to input stimuli alone, contribute to sustaining perception-action cycles (Rosenbaum, 2005). Even though motor control lies at the heart of emotional and cognitive neuroscience, it has received little attention (Rosenbaum, 2005). To this end, processes that underlie movement planning and coordination are largely immune to conscious inspection, and motor timing is not a ubiquitous system, but involves distinct systems that process time intervals in functionally specific areas and activate task dependent networks (Bortoletto, Cook, & Cunnington, 2011). Driving a car, for example, requires precise timed behaviour to determine the initiation of a sequence of movements and the timing of sub-movements, and motor timing is considered crucial for successful execution (Bortoletto et al., 2011).

Impulsivity, specifically, has been linked to factors which are negatively correlated with health related actions, such as drug and alcohol use and violence (Hofmann, Friese, & Wiers, 2008; Strack & Deutsch, 2004; Yang et al., 2012). Impulsivity here is defined as the tendency to act rapidly and/or with diminished forethought of negative consequences to others and oneself (for extended reviews refer to Hamilton, Littlefield, et al., 2015a; Hamilton, Mitchell, et al., 2015). A substantial body of research has identified multiple domains of impulsivity (Hamilton, Littlefield, et al., 2015). One prominent construct of impulsivity is *Rapid Response Impulsivity* (RRI). RRI is characterized by immediate action tendencies without foresight and a lack of context (Hamilton, Littlefield, et al., 2015).

Individuals who are highly impulsive are at a greater risk of developing psychiatric disorders compared to individuals who are not as impulsive. Impulsivity has been identified as

a core deficit in a number of neuropsychiatric disorders, including attention deficit hyperactivity disorder (Rubia, Halari, Christakou, & Taylor, 2009), personality disorders (Arce & Santisteban, 2006) and substance use disorders (Arce & Santisteban, 2006; Berlin & Rolls, 2004; Brighthouse et al., 2013; Coskunpinar & Cyders, 2013; Moreira, Pinto, Almeida, & Barbosa, 2016; Rubia et al., 2009; Wittmann & Paulus, 2008).

In addition to increased impulsivity, motor timing deficits have been found in a variety of psychopathological conditions (Wittmann & Paulus, 2008). Motor timing, which is defined as a component of temporal processing, regulates the generation of timed motor responses (Mauk & Buonomano, 2004). Motor timing deficits have been reported in individuals diagnosed with schizophrenia (Delevoye-Turrell et al., 2007, 2012; Wilquin & Delevoye-Turrell, 2012); Parkinson's disease (Parker, Lamichhane, Caetano, & Narayanan, 2013); attention-deficit/hyperactivity disorder (predominantly hyperactive/impulsive presentation) (Noreika, Falter, & Rubia, 2013; Rommelse et al., 2008; Rubia et al., 2009); and substance use disorder (Wittmann et al., 2007). The co-occurrence of impulsivity and motor timing deficits has led to questions being raised about whether impulsivity represents a fundamental deficit in neurobiology, or a functional cognitive deficit (Cyders, 2015.; Wittmann et al., 2011). Emerging evidence suggests that high impulsivity may be a result of timing deficits in clinical and non-clinical populations (Moreira et al., 2016; Pine et al., 2010; Rubia et al., 2009; Wittmann et al., 2007; Wittmann & Paulus, 2008).

Experimental motor timing paradigms addressing this question have been developed in schizophrenia. Motor timing deficits have only been found in tasks of higher order timing complexity, while lower order timing abilities were intact (Delevoye-Turrell et al; 2015; Weibel et al. 2015; Delevoye-Turrell et al. 2013). Based a growing body of literature linking motor timing abilities and cognitive functioning (Falter & Noreika, 2011; Neufang, Fink, Herpertz-Dahlmann, Willmes, & Konrad, 2008), these findings may potentially explain the characteristic distortions of sense of agency and dysfunctional social interactions in individuals with schizophrenia (Wilquin & Delevoye-Turrell, 2012).

A growing body of research suggests that timing abilities and impulsivity are linked through shared neural circuitry (Kotz, Brown, & Schwartz, 2016; Rubia & Smith, 2004) and that time and timing are both key impulsive processes (Arce & Santisteban, 2006; Wittmann & Paulus, 2008). Impulsive individuals have been found to be more sensitive to time constraints (Masters, Poolton, Maxwell, & Raab, 2008), experience time differently (Wittmann & Paulus, 2008), and are less able to time their actions (Moreira et al., 2016). However, there is a dearth of literature on timing deficits associated with impulsivity in non-pathological samples (Pine et al., 2010) and in disorders characterised by impulsivity (Moreira et al., 2016). Impulsivity has, in fact, been almost exclusively assessed in pathological populations (Moreira et al., 2016). To our knowledge, differences in motor timing abilities (Delevoeye-Turrell et al., 2007, 2012; Wilquin & Delevoeye-Turrell, 2012) have not been investigated in non-pathological individuals who exhibit high levels of RRI. Comparison of motor timing abilities in high versus low RRI individuals could lead to better understanding of the role of these tendencies in clinical disorders (Hamilton et al., 2015).

Our main aim was to assess motor timing abilities (higher versus lower order) in non-pathological adults exhibiting high RRI as compared to low RRI. Our secondary aim was to test the test-retest reliability of the motor task battery. Specifically, we aimed to assess RRI individuals with high inhibitory errors versus those with low inhibitory error rates. We hypothesised that RRI would (i) not be associated with the ability to plan and initiate simple motor actions (lower order- single target) but would have an effect on the cognitive and temporal control of more complex sequential motor actions (higher order-multiple targets). We predicted that (i) high RRI would affect the capacity to, firstly, initiate and then structure, organise and plan an action towards visual targets (higher order motor deficits). We predicted that self-initiated actions to external stimuli are timed (synchronised), more poorly in both time and space in individuals with high RRI compared to individuals with low RRI. This would be expressed through (i) poorer pointing fluency [inter response interval error rates] and (ii), accuracy [synchronisation error rates] of timed responses, as well as (iii), higher spatial errors

and lower contact times in individuals with high RRI levels. With regards to inhibitory capacities, we expected (v) differences in cognitive control between individuals with high and low RRI. Lastly, we expected (vi) a satisfactory test-retest variability over time on all tasks.

3.3 Methods

3.3.1 Participants

Thirty-seven healthy Dutch participants were recruited through convenience sampling in and around Amsterdam (the Netherlands). Participants who expressed an interest in participating were first screened through a telephonic interview for eligibility. After written consent was obtained, face-to-face diagnostic and behavioural assessments were undertaken. To be included, participants had to be between 18 and 55 years, free of any current or past personal or family history of psychiatric and/or substance use disorders, as defined by the DSM-IV. Neurological disorders (e.g. brain trauma with loss of consciousness) and endocrine disorders were also exclusion criteria.

All measures were administered in Dutch, and all 37 participants underwent a quick diagnostic assessment, completed a series of self-reported behavioural questionnaires, and underwent neuropsychological and motor task testing with a researcher trained in neuropsychology. Gender, age, IQ, and handedness were assessed with a self-administered demographic questionnaire. The Mini International Neuropsychiatric Interview version 5 (MINI-5) was used to assess for the presence or absence of psychiatric disorders. The MINI is a semi-structured clinical interview based upon the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 2000) and the International classification of Diseases (ICD)(WHO, 1992) diagnostic criteria for mental disorders (Sheehan et al., 1998).

3.3.2 Procedure

The data used in this study derived from a larger study examining the prognostic value of motor timing in Substance Use Disorders (Young et al, 2016). Following screening, two study visits were scheduled at the Academic Medical Centre, Amsterdam, the Netherlands, i) a pre-assessment including a clinical semi-structured interview (20 min), neuropsychological testing (20 min) and the experimental motor task (15 min) session, (ii) a second visit at 8 weeks repeating the neuropsychological and motor task batteries.

All assessments were conducted in a structured manner by either the PI, or a trained research assistant. One research assistant was appointed for a period of 2 years. For quality control, all questionnaire and task performance scores, including data entry, were cross checked by both the PI and the research assistant. For the administration of all assessments, standard Operating Procedures (SOPs) were followed. Task instructions were read out in the same way to each participant (for the SOPs and instructions that were read out for the neuropsychological testing, see appendix A; for Motor task testing, see appendix B). The same order of assessment was used for each visit and for each participant.

HC participants were individually tested in a quiet room located at the Academic Medical Centre, Amsterdam, during a test session lasting approximately one hour. During this session, questionnaires were administered. Subsequently, participants were asked to perform all tasks in a fixed order. Upon completion, participants were compensated for their participation (10 euros).

3.3.3 The Stop Signal Reaction Task

There are two components to RRI distinct inhibitory errors i) the failure to refrain from action initiation and ii) the failure to stop and on-going (or pre-potent) action (Hamilton, Littlefield, et al., 2015). The latter is typically measured with the Stop Signal Task (SST), as described by van den Wildenberg et al. (2006); in the present study, we used the SST to determine three contrasting degrees of Rapid Response Impulsivity. The SST is a 2-choice

reaction time task consisted of a green arrow (rectangle: 2.0 x 1.0 cm; triangle: 1.5 cm height x 2.0 cm base), which was presented in the middle of the screen for a maximum duration of 1500 ms. Participants were told to press the left key on the computer keyboard with their left index finger as quickly as possible when the arrow pointed to the left and the right key with their right index finger when the arrow points to the right (go-trial). Arrow direction was pseudo-randomly determined with both directions presented equally often. Arrow presentation was terminated by the participant's response. In 25% of the trials, the green arrow turned red, thus notifying participants to inhibit their response (i.e. stop-signal that participants should refrain from pressing the response key).

3.3.4 Motor timing: Action-based timing tasks

The motor tasks consisted of a series of reaction-prediction visuo-motor pointing tasks to measure different aspects of motor timing (motor sequencing, synchronisation, and inhibition). The sequential pointing tasks were all designed by Professor Delevoeye-Turrell and her team at the University of Lille, France. These tasks have been used in previous research but not in SUD research (Delevoeye-Turrell et al., 2007, 2012; Dione et al., 2005; Dione et al., 2013; Dione & Delevoeye-Turrell, 2015). For testing, participants were seated in front of a tactile screen (Elo Touch) of 53cm by 36cm by 30 cm which was placed close to the participants' midline in order to avoid muscle fatigue from the repetitive pointing movements. Visual and auditory signals were controlled via a PC with coded software in C++. For a detailed overview of these tasks, refer to Young et al. (2016).

3.3.5 Reactivity: the Motor reaction task

When it comes to accurately executed spaced and timed reactions, subjective representation of time is crucial (Avanzino, Pelosin, Martino, Abbruzzese, & Maurits, 2013; Bortoletto et al., 2011; Bortoletto & Cunnington, 2010). In order to execute an interval in less than a second, the complete structure of the sequence needs to be planned before movement execution (Bortoletto et al., 2011). When the complexity of the movement to be executed

increases, behaviour results in faster movements. Thus, rhythm and movement initiation are processed into an action plan before the movement occurs (Bortoletto & Cunnington, 2010). Measuring reaction and movement time abilities, whilst carrying out movement sequences, in milliseconds, and in increasing complexities, allows for the measurement of motor planning abilities. The task used for this purpose, the Motor Reaction Task, evaluated this ability using a simple finger-pointing task to visual dots presented on the touch screen.

Participants were required to lift (action initiation- measured as Reaction Time) and touch (action execution- measured as Movement Time) one dot (condition one), a series of two (condition 2) or of 3 dots (condition 3). Manipulation of the complexity (the number of dots) of the motor sequence provides the means to assess lower order timing mechanisms (one target) and higher order mechanisms (2 and 3 dots) through the capacity of participants to structure, organize and plan an action through time and space by ensuring accurate pointing in combination with fast movements. Condition one was designed to measure lower order mechanisms of movement initiation and execution, whereas conditions 2 and 3 were designed to measure higher order mechanisms through increased complexity which requires structuring and planning of motor timing. Participants were instructed to start with the index finger of the dominant hand placed on the square starting zone which is situated at the bottom left edge of the screen. As soon as a black dot appears on the screen, the task is to lift of from the central target (square) and touch the target(s) as fast as possible. Three levels of complexity were counter-balanced: one target, two-target or three-target conditions. With regards to general motor timing abilities, we expected to find decreased motor movements with increasing sequence complexity (number of targets) for all participants.

3.3.6 Synchronisation: the Spatial-tapping task

Sensory motor synchronization is defined as the ability to Synchronise motor output with sensory input (Iversen & Balasubramaniam, 2016). Synchronisation tasks entail finger tapping and circle drawing paradigms (Delevoeye-Turrell et al., 2012; Repp & Su, 2013) and

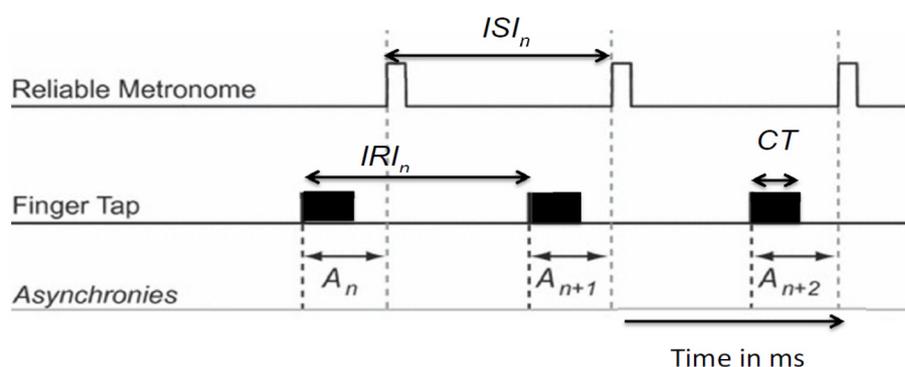
measure the coordination of Synchronising rhythmic movements to an external rhythm (for a review, see Repp, 2013). The Spatial-tapping task (Dione et al., 2013), a hybrid finger tapping-circle drawing task, evaluates how well self-initiated actions to external stimuli are timed (synchronised) in both time and space.

We measured pointing accuracy in time and space as well as error in fluency and accuracy. Six black dots were presented on a tactile screen display in a circle of 100 mm apart. The instruction was to touch each target, one after the other, starting from the bottom right target and moving counter-clockwise using the right index finger (fist closed). Each condition was constituted of a series of sixty taps of, in total, 5 trials. The total duration of the task was approximately 10 minutes. There were two experimental conditions: one using the participants' 'spontaneous' rhythm, and the other where different tempi (ISI= 1100m/sec; 1000m/sec, 900m/sec, 800m/sec, 700m/sec, 600m/sec, 500m/sec, 400m/sec, and 300m/sec) were fixed in terms of inter stimulus intervals (ISI). The ISI is considered an important independent variable in timing research (Repp & Su, 2013).

In condition two, the auditory rhythm was used to pace their actions. After listening to the tones for 5.5s, participants started tapping for a total trial duration of 35s. Timing performances on this task were measured through Inter-response interval errors (IRI error) and Synchronisation errors (Asynchrony) were measured through the difference between onset of a tap and the time of onset in the external rhythm. The IRI was measured as the time intervals between the start of two successive taps and computed as the percentage of absolute difference between each IRI and the reference inter-onset interval (ISI) of a given trial. Refer to Figure 3.1 for a visualisation of the two timing variables (IRI errors and Synchronisation errors). Spatial performances were measured through the measurement of endpoint distributions of pointing actions and were plotted as a function of each visual target position. The mean spatial error (SE) of these spatial ellipses was used as an indication of spatial performances (Dione & Delevoeye-Turrell, 2015). The control of pauses was measured

through contact time (CT) and defined as the time of finger contact with the touch screen. This measure (in m/sec) was used as an indicator of the amount of voluntary pauses in the gesture.

Figure 3-1 Visual overview of Inter response interval, Inter Stimulus interval, Asynchrony and Contact Time



Note. IRI; Inter response interval, ISI; Inter Stimulus interval, A; Asynchrony, CT, Contact Time

3.3.7 Decision-making: The Go-nogo task

In order to achieve positive outcomes in the future and function effectively, the urge for immediate gratification has to be postponed and goal directed behaviour given preference (Zimbardo & Boyd, 1999). To do this effectively and efficiently, cognitive control is necessary. Flexible goal-directed behaviour requires an adaptive cognitive control system for selecting contextually relevant information and for organizing and optimizing information processing. A modified version of the Go-nogo paradigm was designed to measure reaction times through a tactile touch of the touch screen. The starting zone is situated at the bottom left edge of the screen. The target is a white circle with a black letter or one-digit black number, and participants were instructed to act as fast as possible (Go) or refrain from acting (Nogo), depending on the condition of the task. In the first condition, the task was to tap the target that

appears as fast as possible (100% Go). In the following blocks, participants were instructed to react and tap the target as fast as possible also, but only if the target is a letter (50 % Go). If the target is a number, they were instructed to refrain from reacting. Numbers and letters were presented in semi-random order. The targets were presented for 5s on the screen, with a random phase lag of ± 300 m/sec in order to avoid anticipatory responses. To assess cognitive control, the reaction times obtained after a Go Target (of both Go (1) and Nogo (2) conditions), after a Nogo Target, and after a Nogo Target error (i.e. touched the Nogo Target) were used. Cognitive control was measured through decision making (reaction time after Go Targets and Nogo Target) and adaptability (reaction time after a Nogo Target Error). We expected to be expressed as a measurable attempt to avoid making error, or adapting after an error has been made through faster reaction times after a Go Target compared to reaction times after a Nogo Target and a Nogo Target Error indicating control over behaviour.

3.4 Analysis and Results: Part 1

3.4.1 Data Analysis

We examined the test-retest effects of the action-based timing test battery. The intra-class correlation coefficient (ICC) was used as a reliability metric to assess the degree of consistency between session 1 and session 2 (8 weeks).

3.4.2 Test-retest reliability of the Impulsivity test battery

Please see Table 1 for an overview of means and standard deviation of all motor tasks for the population as a whole. With regard to the Reaction-Movement Time Task, a good degree of reliability was found between the two sessions. The average reaction time ICC was .705 (95% CI=.612; .776, $r=.71$, $p<.01$). With regard to movement times on this task, a good degree of reliability was found between the two sessions. The average measure ICC was .695 (95% CI = .612; .762, $r=.69$, $p<.01$). With regard to the Synchronization Tapping task, good

reliability was found on IRI error percentages between the two sessions. The average ICC was .742 (95% CI =.685; .791, $r=.74$, $p<.01$). A good degree of reliability was found on Asynchrony between the two sessions with the average ICC .634 (95%CI=.559; .698, $r=.63$, $p<.01$). A good degree of reliability was found on CTs between the two sessions with the average ICC was .762 (95% CI =.708; .808, $r=.77$, $p<.01$). A good degree of reliability was found on Spat error percentages between the two sessions. The average ICC was .726 (95% CI =.661; .779, $r=.73$, $p<.01$). With regard to the Go- Nogo task, excellent reliability was found between the reaction times of the Go stimuli between the two sessions. The average ICC was .870 (95% CI =.792; .919, $r=.86$, $p<.01$).

Table 3-1 Motor task performances of sample as a whole

			All participants			
			Pre Assessment		Post Assessment	
			<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Inhibitory Motor Control	<i>Reaction Time)</i>	<i>After Go</i>	.53	.06	.54	.06
		<i>After Nogo</i>	.59	.09	.58	.09
		<i>After Nogo</i>	.53	.06	.57	.11
		<i>error</i>				
Sensorimotor Control						
<i>Time</i>	<i>Asynchrony (%)</i>	-.04	.06	-.05	.05	
	<i>IRI error (%)</i>	6.13	1.65	6.8	1.77	
<i>Space</i>	<i>Contact Time (ms)</i>	.17	.09	.17	.11	
	<i>Spatial Error (%)</i>	13.00	3.70	13.58	3.70	
Motor Coordination		.40	.06	.38	.07	
	<i>Reaction Time</i>					
	<i>Movement Time</i>	.36	.08	.35	.09	

3.5 Analysis and Results: Part 2

In the second step, the sample was stratified by RRI status based on global scores on the SSRT task, at the first test session only. The 65th percentile of global scores was used to determine the cut-off for the high RRI group whilst the 25th percentile was used to determine the cut-off for the low RRI group. Participants with scores between the 25th and 65th percentile were excluded from further analyses ($n=11$). Hence, in the present study, cut-offs were based on SST scores: SSRT scores of 115.25- 184.24, for the low RRI group and SSRT 224.85 – 300.98 for the high RRI group.

To verify the validity of RRI group stratification, an ANOVA was run on global SSRT scores. Results revealed a significant difference between low and high RRI groups ($F(1,46) = 137.46, p < 0.001$) with a higher score in the high RRI group ($M = 444, SD = 75$) than in the low RRI group ($M = 413, SD = 108$). Normality assumptions were checked and adequately addressed. Analysis of Variance (ANOVA) was conducted for motor task outcomes. Significant interactions were assessed using the post hoc LSD test. A p-value of .05 was considered statistically significant. All statistical analyses were performed using Statistica Software version 13.1.

3.6 Results

3.6.1 Sample

For an overview of sample demographics, see Table 3-1. No significant group differences were found between the high RRI and low RRI groups on any demographic characteristics. The age of the participants ranged from 20 to 55 years ($M = 38, SD = 14.5$) with the average years of education being 15 years ($SD = 2.8, range 12-16$ years). Thirteen participants were included in the low RRI group and thirteen participants in the high RRI group, for sessions 1 and 2, respectively.

Table 3-2 Sample characteristics

N=26	Total		Low RRI		High RRI	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>N</i>	<i>%</i>
Gender						
Male	21	57	9	70	7	54
Female	16	43	4	30	6	46
Caffeine use						
Yes	29	78	10	77	13	100
No	8	22	3	23	0	0
Nicotine use						
Yes	6	16	3	23	1	8
No	31	84	10	77	6	92
Handedness						
Right	34	92	13	100	11	84
Left	1	3	0	0	1	8
Ambidextrous	2	5	0	0	1	8
Marital Status						
Married	7	19	4	30	2	17
Single	22	59	5	39	9	75
Stable relationship	7	19	3	23	2	17
Widowed	1	3	1	8	0	0
Employment						
Employed	25	68	5	39	1	14
Unemployed	12	32	8	61	6	86

3.6.2 The Motor reaction task

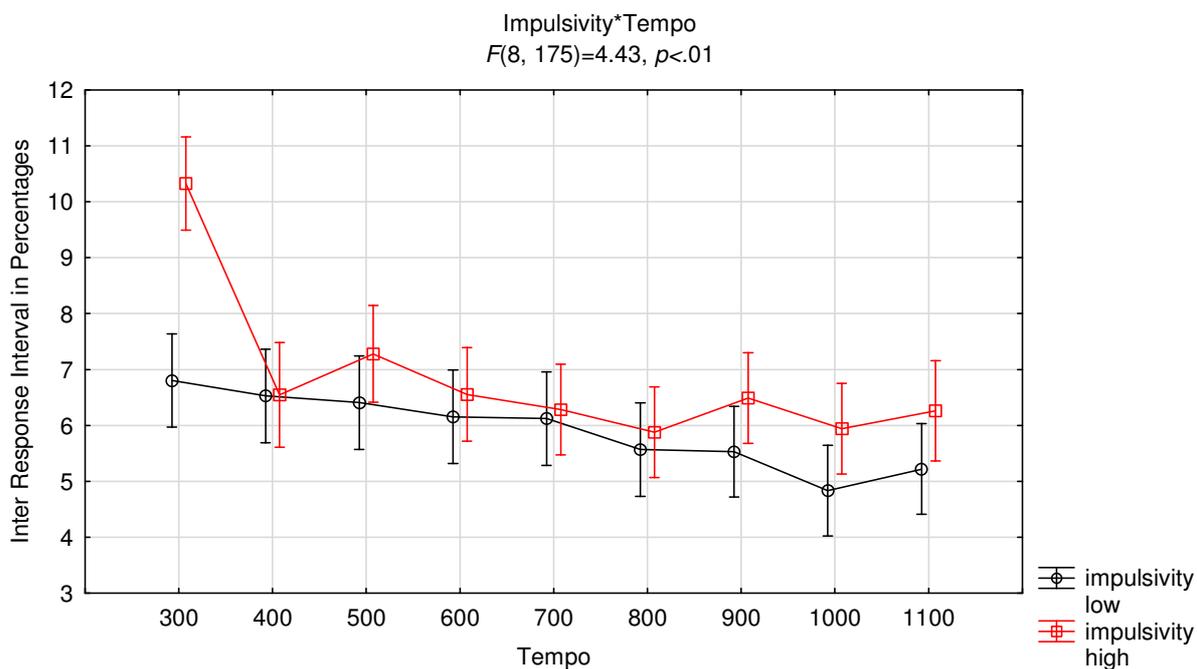
No main effect for RRI was not found. No difference in action initiation of motor behaviour was found between the groups; the low RRI group moved at similar speed ($M=.30$, $std\ error=.01$) as the high RRI group ($M=.29$, $std\ error=.01$). There was a main effect for Condition ($F(2, 44) = 14.109$, $p < .01$). Post hoc analyses confirmed a significant difference in mean reaction times between one target and two target conditions ($mean\ diff=.042$, $std\ error .010$, $P < .01$), and one target and three target conditions ($mean\ diff=.053$, $std\ error=.010$, $p < .01$), but not between the two and three target conditions. No interaction effect was found between Reaction Time and RRI group. No main effect was found for IRI on movement times. There was a main effect of Condition on movement times ($F(2, 44) = 78.71$, $p < .01$). Post hoc analyses confirmed a significant difference in mean reaction times between one target and two target conditions ($mean\ diff=.018$, $std\ error .016$, $p < .01$), and one target and three target conditions ($mean\ diff=.019$, $std\ error=.017$, $p < .01$) but not between the two and three target conditions. No interaction effect was found for Movement Time and RRI group.

3.6.3 The Spatial-tapping task

3.6.3.1 Time: Inter-response interval

A main effect for RRI was found on IRI error percentages ($F(1, 24) = 6.29$, $p = .01$) - error rates for the low RRI group were lower ($M=5.9$, $Std\ error=.3$) compared to the high RRI group ($M=6.8$, $Std\ error=.3$). A main effect for ISI on IRI error was found ($F(8, 17) = 14.3$, $p < .01$). IRI errors decreased at slower tempi. This decrease in error was significant for ISI300 compared to all other tempi (ISI, 400 – 1100m/sec). An interaction effect was found on IRI error percentages, ISI and RRI groups ($F(8, 17) = 4.431$, $p < .01$) (see figure 3.2). Post hoc analyses revealed that there was a significant difference between RRI groups at ISI 300. The low RRI group had lower error percentages ($M=10.31$, $SD= 3.5$) compared to the high RRI group ($M=6.6$, $SD=1.5$).

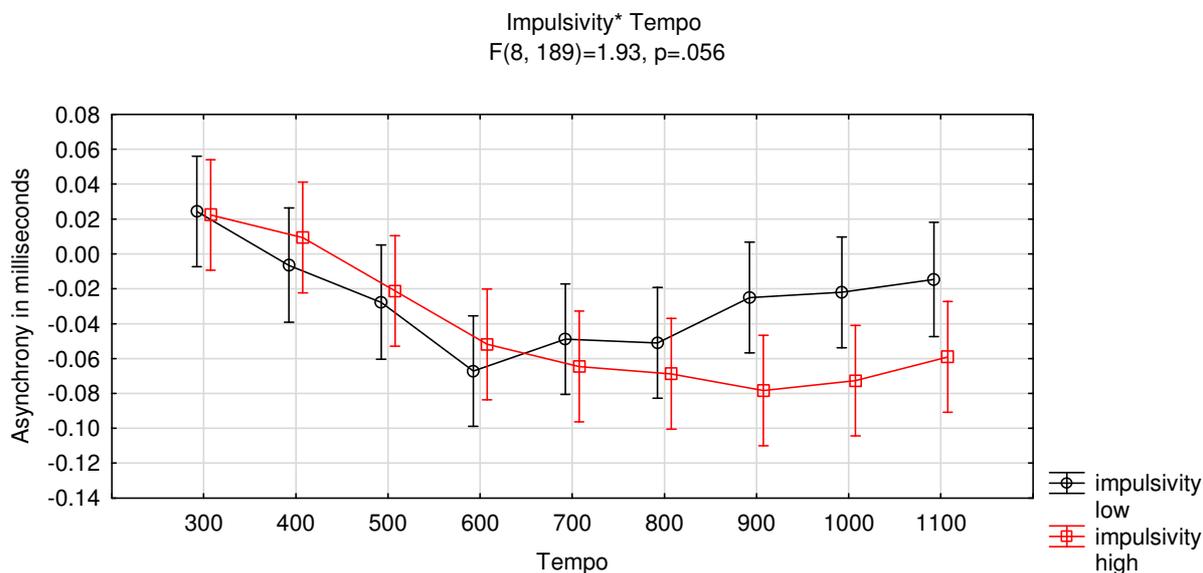
Figure 3-2 Inter response interval error differences between low and high impulsive groups



3.6.3.2 Time: Asynchrony

No main effect was found for Impulsivity. A main effect was found for ISI ($F(8,19) = 8.89, p<.01$). Negative asynchronies were observed for tempi faster than ISI 400. A trend towards significance was found for ISI and Group ($p=.056$) (see figure 3.3). Larger negative asynchronies for tempi with an ISI slower than 700 in the high RRI group were found. See Figure 3.4 for an overview of these results.

Figure 3-3 Asynchrony performance differences between high and low impulsive individuals



3.6.3.3 Space: Spatial Error and Contact Time

No effect for RRI was found. A main affect was found for ISI on SE ($F(8.16) = 58.10$, $p < .01$), with individuals making more SE at higher tempi. At ISIs 300, 400 and 500, spatial errors differed in all combinations ($p < .01$). No interaction effect was found for spatial errors, ISI and RRI group; however, on average, the high RRI had higher spatial error rates on all tempi. No significant main effect was found for RRI on CT. There was a main effect for ISI on CTs ($F(8.17) = 8.62$, $P < .01$). Post hoc analyses revealed that CTs were longer for longer ISI, which were significantly longer at ISI300 and ISI600-1100 milliseconds, ISI400 and ISI800-1100 milliseconds, and ISI500 and ISI800-1100 milliseconds (all comparisons $p < .01$). No interaction effect was found between RRI and ISI on CTs. The high RRI group did have shorter CTs on all ISI.

3.6.4 The Go-nogo task

No main effect for RRI was found on the Go-nogo task. A main effect for cognitive control on Target was revealed ($F(2, 32) = 5.86, p < .01$). Individuals responded significantly faster after a Go Target compared to a Nogo Target ($p < .01$). Surprisingly, Individuals also responded significantly faster after a Nogo Target Error compared to a Nogo Target ($p < .01$). There were no differences in reaction times on trials following a Go Target and a Nogo Target Error. No interaction effect was found between RRI and reaction times on different Targets.

3.7 Discussion

This study found that non-pathological RRI affects the strategic coordination of temporal processing of voluntary motor behaviour. Our results show no differences in motor planning between high and low RRI groups and cognitive control using the Go Nogo task. With regard to errors in response intervals, there were significant differences between the high and low RRI groups and, on average, high RRI individuals had a higher error percentage than low RRI individuals, which was statistically significant at fast tempi. The high RRI group was also less able to synchronise sequential movements, which was significant at slower tempi. We conclude that high and low RRI individuals do differ with regards to motor timing abilities but that differences seems to indicate specific and not general timing deficits.

Contrary to much of the RRI literature, we did not find elevated reaction times (for a review see Arce & Santisteban, 2006) in individuals with high RRI. This may be due to great variation in specificity of the impulsivity construct and variation in the measurement tools used to assess impulsivity (Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015). We found specific deficits in synchronisation abilities between high and low RRI groups. More errors in motor timing were made at slower tempi by the high RRI group, thereby indicating that RRI may affect the timing accuracy and fluency but not decision making and planning abilities. Finally, no test-retest variability was found for these tasks at retest (8 weeks).

In sum, we found that RRI modulates fluency performance only when motor sequences are performed at slow tempi and more timing accuracy deficits at slower tempi. Hence rapid response RRI can only be revealed when effort to perform is required. We found that RRI does not affect generalized motor timing. The capacity to control, plan and execute actions are initiated and completed as good as individuals with low levels of RRI. RRI seems to only affect the ability to modulate behaviour when cognitive difficulty increased. This raises an interesting point related to the problem of motor adjustments when driving a car, for example.

From these results, it would seem that individuals with high RRI may experience problems when needing to drive very slowly (e.g. in the city) or very fast (on highways). In sum, more research on impulsivity in non-clinical populations is needed (Hamilton, Littlefield, et al., 2015; Moreira et al., 2016), with temporal processing considered in new research paradigms (Wittmann & Paulus, 2008). Additionally, issues of the specificity of timing deficits and impulsivity constructs (Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015; Wittmann & Paulus, 2008), and the contribution of impulsivity to the aetiology of psychiatric disorders (Cyders, 2015), require further investigation. The novel findings of this study suggest that further scrutiny of the deficits often implicated in RRI individuals is warranted.

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4 Prognostic Value of Motor Timing in Treatment Outcomes and Relapse in Patients with Alcohol- and/or Cocaine Use Dependence in a Rehabilitation Program

Chapter 4 presents the findings from the primary aims of this study. The paper aims to assess motor timing performances in light of clinical outcomes (defined as Self Perceived Self Efficacy to Abstain from Substance Use [Alcohol and/or Cocaine]). The findings have been presented here in the format of a publication, as this section will be submitted to a peer reviewed Journal.

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4.1 Abstract

Introduction: Individuals with SUD often have cognitive deficits in multiple domains, with recovery times of up to one year. These deficits influence treatment outcomes and abstinence. In addition, motor timing deficits have been found in SUD, but to our knowledge, timing deficits have not been investigated with regard to treatment outcome and relapse. **Methods:** This prospective study tested the theoretical basis for prognostic indicators in SUD with regards to motor timing (measured in terms of treatment response and relapse). The study sample consisted of 74 abstinent in-patients at a private treatment programme for drug/alcohol dependence at the Momentum Mental Healthcare South Africa clinic in Somerset West, South Africa, diagnosed with alcohol and/or cocaine dependence. Participants were tested at three points (i) Within 72 hours of the start of the treatment programme (ii) after completion of the treatment programme at eight weeks (measure of treatment response) through filling out self-report questionnaires and experimental motor task testing, and (iii) a third visit followed through a telephonic interview at 12-months (measure of relapse). **Results:** Motor timing alone predicted 27 percent of the variance in total score change on the Alcohol Self-Efficacy Scale. Specifically, spatial errors, synchronisation errors and IRI errors at baseline predicted self-efficacy at treatment completion. With regard to motor timing, change in cocaine self-efficacy scores at treatment completion explained 25 percent variance. Specifically, spatial errors and contact times were predictive at very high tempi (300m/sec). The sample size at 12 months did not allow for further analyses of prognostic values. **Conclusions:** This research provides novel insights on the prognostic value of treatment outcomes and relapse in SUD. To our knowledge, it is the first study of its kind. The results of this investigation show us that motor timing holds prognostic value with regard to treatment outcomes. Motor timing predictors for relapse remain unclear. This requires investigation going forward.

4.2 Background

4.2.1 Cocaine and Alcohol use

Alcohol and cocaine are amongst the most widely abused substances worldwide (The Global Drug Survey 2015 findings | Global Drug Survey, n.d.). Over the past decade, cocaine use and abuse has reached epidemic proportions (Gillen et al., 1998), and in Europe alone, alcohol is a leading preventable cause of ill health (Rehm, Shield, Rehm & Frick, 2012). These substances are known to affect the brain through the mesolimbic dopamine (DA) reward circuitry. Substances of abuse increase DA in the reward centre and lead to neurobiological changes associated with chronic excitation of DA pathways (Goldstein & Volkow, 2002; Volkow & Fowler, 2000) in Substance Use Disorders (SUD) (Dackis & O'Brien, 2001; Goldstein, Leskovjan, & Hoff, 2004; Goldstein et al., 2009; Rehm et al., 2012; Volkow & Baler, 2014). Chronic exposure to substances also leads to structural and functional brain disturbances (Bühler & Mann, 2011; Moselhy, Georgiou, & Kahn, 2001; Oscar-Berman & Marinkovic, 2003; Scheurich, 2005; Verdejo-García, Perales, & Pérez-García, 2007; Volkow et al., 2010) which underlie the cognitive decline and behavioural changes found in SUD (Bates, Bowden, & Barry, 2002; Goldstein & Volkow, 2011; Miller, 1991).

4.2.2 Neurocognitive deficits in SUD

Individuals with SUD suffer from cognitive deficits (Spronk, van Wel, Ramaekers, & Verkes, 2013; Stavro, Pelletier & Potvin, 2013). Even those who seem clinically 'intact' with no apparent dysfunction exhibit neurocognitive deficits (Mosely et al., 2001). Recent studies on the neurocognitive effects of long-term cocaine and alcohol use show that, instead of specific impairments, dysfunctions occur for a wide array of cognitive domains (Stavro, 2012; Spronk, van Wel, Ramaekers, & Verkes, 2013). Use of these substances is associated with deficits in frontal lobe and striatal functioning (Spronk et al., 2013, Mosely et al., 2001) through alteration in activation of the cortico-limbic reward circuit (Welberg, 2011).

Aspects of self-control, delayed self-gratification, drive inhibition and anticipation of the consequences all require the functional integrity of executive pre-frontal cortical system (Lyvers, 2000). Breakdown of orbitofrontal cortical communication may, in part, explain the decrease in motivation and self-control experienced in individuals with SUD (Dackis & O'Brien, 2001; Welberg, 2011). However, the direct influence of neurocognitive deficits on recovery, and sobriety remains unclear (Bates et al., 2002). Relapse can occur weeks, months and even years after use (Welberg, 2011), and long-lasting changes in brain regions involved in reward processing may contribute to this phenomenon (Welberg, 2011). Proper decision-making, delay of instant gratification, and impulse control abilities have all been shown to be vital to maintaining abstinence and are known to influence treatment outcomes (Fox et al., 2007; Pitel, 2007, Laurance et al., 2009). Owing to limited pharmacological treatment options, many clinicians worldwide rely solely on psychosocial approaches (Dackis et al., 2001). Cognitive deficits experienced by individuals with SUD may, therefore, be of broad relevance in psychosocial adaptation, and more specialised research that informs clinical practice and guides future research is needed to improve and broaden treatment options.

4.2.3 Motor timing

From an existential viewpoint, qualitative experiences of a person's past, present and future, and the subjective apprehension of actual time, as well as intersubjective synchronicity with others, are all conditions that inform individual experience (Moskalewicz, 2016). Motor timing lies at the core of successful execution of timely self-initiated movement sequences (Bortoletto et al., 2011) and is defined as the ability to organize movement according to temporal structures. Motor timing is most often measured in tests of sensori-motor synchronisation, or anticipation in the millisecond or second range (Rubia, 2009). The motor representation of time intervals emerge from the coordinated activity of several cortical regions (Rosenbaum, 2005).

Although there is disagreement as to a precise boundary between short and long time intervals, the timing of short intervals is regulated by 'automatic' systems and longer intervals by 'cognitive' systems (Coslett, Shenton, Dyer & Wiener, 2009). Motor timing requires both time and explicit representation to be coordinated for successful movements (Bortoletto et al., 2011). For example, if an interval between movements is less than a second, the complete structure of the sequence is planned before movement execution, meaning that at higher time constraints, sequence initiation and rhythm are processed before a movement occurs (Bortoletto & Cunnington, 2010).

On a physiological level, it has been found that reciprocal connections between cortical and striatal regions of the brain form neuro-functional circuits involved in the encoding and decoding of temporal structures (Kotz, 2016). Specifically, the DA system and its target neural substrates (Striatum and PFC) are important neural systems with regard to timed behaviour (Brighthouse et al., 2013; Soares, Atallah, & Paton, 2016; Wittmann & Paulus, 2008). Indeed, it has been suggested that DA levels in the striatum, but not the PFC, ventral striatum or hippocampal regions, are crucial for the regulation of timing behaviour (Cheng, Mac Donald & Meck, 2006). A recent review on the contribution of DA signalling to timing accuracy and precision found that the processing of temporal information (in the 100s m/sec to second range) recruits brain regions such as cortico-striatal circuits (Agostino and Cheng, 2016). Time-keeping operations are regulated through DA neurotransmission in the striatum (Rao et al., 2004) and have been shown to be affected in many psychiatric disorders associated with DA dysfunction (Agostino & Cheng, 2016). Individuals with reduced striatal DA receptors have reduced temporal discriminatory accuracy (Kotz, 2016). A recent study in rats found that the direct pharmacological suppression of DA neurons decreased behavioural sensitivity to time and affected the encoding of time variability by DA neurons, concluding that time estimations and judgements are controlled by DA neurons in the midbrain (Soares et al., 2016).

A timing study examining aspects of impulsivity through either pharmacological enhancement of dopamine or placebo showed that by explicitly probing the relationship

between the utility of rewards and their timing, DA increased impulsivity by enhancing the diminutive influence of increasing delay on reward value and its corresponding neural representation in the striatum (Pine et al., 2010). Dopaminergic treatment for Parkinson's disease improves motor timing (Rao et al., 2004). One of the few studies to date that attempted to examine motor timing in stimulant dependent individuals, whilst controlling for possible confounds, found that motor timing deficits are present in this population (Wittmann et al., 2007). The stimulus dependent group showed abnormal motor timing abilities on all timing tasks, except sensorimotor synchronisation. With regard to neuropsychological deficits other than timing, only the overestimation of a relatively long time interval could be explained by impulsivity. These results indicate that stimulant dependent individuals exhibit motor timing deficits that cannot be explained by cognitive deficits (Wittmann et al., 2007).

In sum, individuals with SUD often have cognitive deficits in multiple domains, with recovery times of up to one year (Spronk et al., 2013; Stavro et al., 2013). These deficits influence treatment outcomes and abstinence (Fox et al., 2007; Pitel, 2007, Laurance et al., 2009). In addition, motor timing deficits have been found in SUD (Cheng, MacDonald, Meck, 2006; Wittmann, Leland & Paulus, 2007), but to our knowledge, timing deficits have not been investigated with regard to treatment outcome and relapse. More research is needed to address temporal processing and how deficits translate into functional differences in simple and complex temporal sequencing behaviour (Kotz, 2016). Early detection of motor timing deficits may be predictive of treatment outcome and relapse risk. Cognitive training of motor timing as well as alternative activities that function as distractors to inhibit premature responses may be potentially useful interventions. This prospective study tested the theoretical basis for prognostic indicators in SUD with regards to motor timing (measured in terms of treatment response and relapse). We expected that i) the capacity to structure, organise and plan an action directly towards a visual target (motor reaction task [Task 1]; ii) decision making (Go-nogo task [Task 3]); and synchronisation abilities (Spatial-tapping task

[Task 2]) would be prognostic of treatment outcomes (self-perceived efficacy to abstain from substances) at 8 weeks and possible relapse (yes/no).

4.3 Methods

4.3.1 Sample

The study sample consisted of 74 abstinent patients, aged 18-60, and diagnosed with alcohol and/or cocaine dependence. Patients with a primary diagnosis of alcohol and/or cocaine dependence who were detoxified were included. Patients who met criteria for other substance abuse (lifetime or current) were included, provided that these were not their primary drugs of use/abuse. Patients who met criteria for other substance dependence (i.e. other than cocaine/alcohol) were excluded. For the alcohol group, patients were excluded if they had a current or past history of dependence on cocaine. For the cocaine group, patients with a current or past history of alcohol dependence were excluded.

4.3.2 Procedures

Participants were all inpatients at a private treatment programme for drug/alcohol dependence at the treatment clinic in Somerset West, South Africa. The clinic offers treatment to individuals who are mainly of Dutch nationality, as the main patient referral company is situated in the Netherlands. The comprehensive primary care treatment program, which formed the standard of care for all participants, centres on an 8-week cycle of treatment comprised group therapies, individual counselling, written work and a psycho-educational lecture series. All participants worked individually with a therapist. A full medical examination was conducted on every patient included. This consisted of a physical examination, toxicology and biochemistry work-up by the psychiatric nursing staff.

Participants were tested at three points in time: (i) within 72 hours of the start of the treatment programme, (ii) after completion of the treatment programme at eight weeks (measure of

treatment response), and (iii) at a 12-month follow-up period (measure of relapse). Designated counsellors at the clinic enquired from patients about their potential interest in participating in the study. Only participants who gave written consent and who were eligible upon screening were invited for a first research visit. After written consent was obtained, the Measurements in the Addictions for Triage and Evaluation.2 (MATE.2.10) (Schippers, Broekman, Buchholz, Koeter & Van Den Brink, 2010), a semi-structured diagnostic interview (MINI) (Lecrubier et al., 1997), and a socio-demographic questionnaire was administered. Two study visits were conducted at the clinic. Each of these visits entailed filling out self-report questionnaires and experimental motor task testing. All assessments were conducted in a structured manner by either the PI, or a trained research assistant. One research assistant was appointed for a period of 2 years. For quality control, all questionnaire and task performance scores, including data entry, were cross checked by both the PI and the research assistant. For the administration of all assessments, standard Operating Procedures (SOPs) were followed. Task instructions were read out in the same way to each participant (for the SOPs and instructions that were read out for the neuropsychological testing, see appendix A; for Motor task testing, see appendix B). The same order of assessment was used for each visit and for each participant.

After completion of the first visit, an appointment for a second assessment was made. Both assessments were undertaken within 72 hours of initiation of the treatment program and repeated at the end of the eight weeks (last 72 hours). A telephonic interview using the MATE.2.10 (Schippers, Broekman, Buchholz, Koeter & Van Den Brink, 2010) was used as a follow-up procedure at twelve months to assess relapse.

4.3.3 Measures

Gender, age, handedness, ethnicity, education, family history of substance dependence, previous admissions/counselling/therapy history, drug or alcohol usage

(including last intoxication, last drink and last withdrawal), depression, impulsivity and psychopathology were assessed with the following: a self-administered demographic questionnaire, the *Edinburgh Handedness Questionnaire* (EHQ) (Büsch et al., 2010), *The MATE.2.10 Outcomes Measurement* (Schippers, Broekman, Buchholz, Koeter & Van Den Brink, 2010), Mini International Neuropsychiatric Interview version 5 (MINI 5) (Lecrubier et al., 1997), *The Alcohol Use Disorders Identification Test* (AUDIT) (Lundin et al., 2015), and *Drug Use Disorders Identification Test* (DUDIT), (Hildebrand, 2015) *The Alcohol Abstinence Self-Efficacy Scale* (AASE) AND *The Cocaine Abstinence Self-Efficacy Scale* (DiClemente et al., 1994) and the *Beck Depression Inventory* (BDI) (Beck et al., 1988).

4.3.4 Motor timing: Action-Based Timing Tasks

The motor tasks consisted of a series of reaction-prediction visuo-motor pointing tasks to measure different aspects of motor timing. The motor task battery consisted of three sequential pointing tasks for measuring different aspects of motor timing (motor sequencing, synchronisation, and inhibition) designed by Professor Y. Delevoeye-Turrell and her team at the University of Lille, France. These tasks have been examined previously but have not been used in SUD or to evaluate their prognostic value (Delevoeye-Turrell et al., 2007, 2012; Dione et al., 2005; Dione et al., 2013; Dione & Delevoeye-Turrell, 2015). For testing, participants were seated in front of a tactile screen (Elo Touch) of 43cm by 36cm by 30 cm which was placed close to the participants' midline in order to avoid muscle fatigue from the repetitive pointing movements. Visual and auditory signals were controlled via a PC with coded software in C++.

4.3.5 Reactivity: Motor reaction task

Motor timing is the ability to organize movements according to temporal structures and relies on motor representation of time intervals. It is also essential for self-initiated movement

sequences (Bortoletto & Cunnington, 2010). Motor sequencing abilities were evaluated using a simple finger-pointing task to visual dots presented on the touch screen. Participants are required to lift (reaction time) and touch (movement time) one dot (condition one), a series of two (condition 2) or 3 dots (condition 3). Condition one is designed to measure lower order mechanisms of movement initiation and execution, whereas condition 2 and 3 are designed to measure higher order mechanisms of increased complexity which requires structuring and planning of motor timing (for a detailed overview of all motor tasks, please see Young et al., 2016).

The manipulation of the complexity (the number of dots) of the motor sequence thus provides the means to assess lower order timing (one target) and higher order (2 and 3 dots) mechanisms through the capacity of participants to structure, organize and plan an action in time and space by ensuring accurate pointing in combination with fast movements. Participants are instructed to start with the index finger of the dominant hand placed on the square starting zone which is situated at the bottom left edge of the screen. As soon as a black dot appears on the screen, the task is to lift of from the central target (square) and touch the target(s) as fast as possible. Three levels of complexity were counterbalanced: one target; two-target or three-target conditions. In all conditions, the means and standard deviations of reaction and movement time for each individual was calculated. The reaction time was measured as the time between target presentation and finger-lift off of the square. The movement time was measured as the time of lift-off and touch of first target.

4.3.6 Synchronisation: Spatial-tapping task

Synchronising movements to external events are central to adaptive behaviour. A popular research paradigm for the measurement of motor timing abilities are sensorimotor synchronisation tasks. These tasks entail finger tapping and circle drawing paradigms (Yvonne, Repp, Dione; Repp, 2013), measure the coordination of rhythmic movements with

an external rhythm and are frequently used as a way to measure motor timing abilities (for a detailed review on sensory motor synchronisation research see Repp, 2013). Synchronisation errors (asynchrony) are the basic response variables, and asynchrony is defined as the difference between onset of a tap and the time of onset in the external rhythm.

The tempo of the external rhythm is measured in terms of inter-onset interval (IOI) and is considered an important independent variable in timing research. With this task, we aimed to evaluate how well self-initiated actions to external stimuli, present in the environment, are timed (synchronised) using a Spatial-tapping task (Dione et al., 2013). This task measures pointing accuracy in time and space as well as error in fluency and accuracy. On the tactile screen display are six black dots 100 mm apart in a circle. The task is to touch each target, one after the other, starting from the bottom right target, and moving counter-clockwise using the right index finger (fist closed). Each condition is constituted of a series of sixty taps, in a total of 5 trials. The total duration of the task is approximately 10 minutes. There are three experimental conditions. In each trial participants are presented with an auditory rhythm that must be used to pace their actions (ISI= 1100m/sec; 700m/sec, 500m/sec, 400m/sec, and 300m/sec). After listening to the tones for 4.5s, participants start tapping for a total trial duration of 35s. Inter-response intervals (IRIs) were measured as the time intervals between the start of two successive taps. The IRI error was computed as the percentage of absolute difference between each IRI and the reference IOI of a given trial and was used as an indicator of timing (synchronisation) capacity. Synchronisation errors (asynchrony) were measured through the difference between onset of a tap and the time of onset in the external rhythm.

4.3.7 Decision making: Go-nogo task

In order to achieve positive outcomes in the future and function effectively, impulsive urges for immediate gratification have to be postponed and goal directed behaviour has to be given preference (Zimbardo & Boyd, 1999). To do this effectively and efficiently, cognitive control is necessary. Flexible goal-directed behaviour requires an adaptive cognitive control

system for selecting contextually relevant information and for organizing and optimizing information processing. A modified version of the Go-nogo paradigm was designed which measured reaction times through a tactile touch of the touch screen. The starting zone is situated at the bottom left edge of the screen. The target is a white circle with a black letter or one-digit black number and participants are instructed to act as fast as possible (Go) or to refrain from acting (Nogo), depending on the condition of the task. In the first condition, the task is to tap the target that appears as fast as possible (100% Go). In the following blocks, participants are instructed to react and tap the target as fast as possible only if the target is a letter (50 % Go). If the target is a number, they have to refrain from reacting. Numbers and letters are presented in semi-random order. The targets are presented for 5s on the screen, with a random phase lag of ± 300 m/sec in order to avoid anticipatory responses. We categorized the Go trials as follows: (1) a correct Go trial (2) a correct Nogo trial and (3) an incorrect Nogo trial to assess cognitive control reaction time obtained after a Go stimulus (of both Go (1) and Nogo (2) conditions), after a Nogo stimulus, and after a Nogo stimulus error (i.e. touched the Nogo target).

4.4 Data Analyses

Backward step-wise regressions were conducted to establish the best fit of motor timing variables regarding their predictive power on self-efficacy total score change at 8 weeks. Best subset regressions were used to select the best fitting models out of top 20 models with the least number of predictor variables.

4.5 Results

4.5.1 Sample

4.5.1.1 Demographics

All participants included in this study completed treatment. All participants were right handed, ($n=59$) 80 percent were male, and the mean age was 36.6 yrs old ($SD= 10.5$, $mode= 27$, range 19-60). Forty-two participants (59%) were employed, and 27 participants (36.5 %) were receiving unemployment benefits. Half of the participants were single, 13 participants (20%) percent were divorced and 28 participants (40%) have children.

4.5.1.2 Clinical Characteristics

Patients with comorbid disorders at the beginning of their treatment were excluded from entry into the study; however, at discharge (8 weeks), some participants had been diagnosed with comorbid disorders ($n=10$, 15% Axis 1 Psychiatric disorder; $n= 15$, 20% Axis 2 Personality Disorder; $n=5$, 7% both Axis 1 and 2). Previous outpatient treatment had been attempted by $n= 38$ (51.4%) while $n= 23$ (31%) had received psychotherapy, 12 participants (16.2%) had previously been admitted to psychiatric inpatient care (non SUD- majority due to a failed suicide attempt), and for 21 participants (29%), this was the second (or more) attempted inpatient rehabilitation. Upon admission, 23 (31%) of the participants had a positive alcohol test (through a Breathalyzer examination) while 38 participants (54%) had a positive drug test (Cocaine $n=25$ (33%), Benzodiazepine $n=8$ (10.8%), Cannabis $n=5$ (6.8%), and Amphetamine $n=1$ (1.4%). Drug use other than Cocaine and/or Alcohol was minimal, with 9 percent using XTC, other stimulants (e.g. Speed, Methamphetamine 15 percent) and sedatives (prescription 12 percent) in the 30 days before admission to treatment. For 22 participants (30%), detoxification prior to admission to the clinic was necessary. Severity of psychiatric comorbid symptoms was below threshold on the Anxiety, Depression and Stress scale (MATE Q2 total score of < 60) ($m= 41.8$, $SD= 25.2$, $mode=12$). Craving symptoms were

minimal at baseline (MATE Q1 total scores of <12) ($m= 7.5$, $SD= 3.9$). A detailed overview of the described clinical measures can be found in table 4.1 and 4.2.

Table 4-1 Clinical and demographic characteristics of all participants

	All patients	
	<i>M</i>	<i>SD</i>
<i>N</i> =74		
Age	37.1	11.1
Alcohol Use in the last 30 days	13.1	10.3
Alcohol quantity used in the last 30 days (units)	12.6	12.3
Cocaine Use in the last 30 days	8.8	10.4
Cocaine quantity used in the last 30 days (grams)	1.5	2.5
AUDIT	19.6	10.7
DUDIT	23.6	13.2
Duration of Use	17.3	10.3
Age of first Use	19.6	6.8
Abstinence in days	14.9	12.2

Note. Results of Separate groups' IQ: Nederlandse Leestest voor Volwassenen indication of intelligence, AUDIT: Alcohol Use Disorder Identification Test, DUDIT: Drug Use Disorder Identification Test; Quality of Life, Sheehan Disability Scale (SDS), Impulsivity, (BIS) Behavioural Inhibition Scale; GAF: Global Assessment of Functioning. MATE 5; Measurements in the Addictions for Triage and Evaluation, Physical Complaints/health related symptoms in the last 30 days; MATE Q1, Measurements in the Addictions for Triage and Evaluation, Craving Scale regarding the last 30 days; MATE Q2, Measurements in the Addictions for Triage and Evaluation, Anxiety, Depression, Stress Scale in the last 30 days.

Table 4-2. Clinical characteristics at baseline and discharge of treatment

N=74	Baseline		Discharge		p
	M	SD	M	SD	
SDS	18.65	7.8	12.6	9.4	<.01
BECK	8.66	6.5	4.8	4.1	<.01
BIS	19.58	11.2	9.3	6.1	<.01
GAF	52.30	8.9	56.8	6.8	<.01
SDS	18.65	7.8	12.6	9.4	<.01
SAWS	8.5	6.5	4.8	4.1	<.01
MATE 5	110.	7.8	4.7	4.4	<.01
MATE 7	21.9	13.2	6.5	6.0	<.01
MATE Q1	7.5	3.9	4.1	2.3	<.01
MATE Q2	41.8	25.2	19.6	18.2	<.01

Note: Results of sample as a whole, SDS: Sheehan Disability Scale, BECK: Beck Depression Inventory, BIS: Behavioural Inhibition Scale; SAWS, Short Alcohol Withdrawal Scale; GAF: Global Assessment of Functioning. MATE 5; Physical Complaints/health related symptoms in the last 30 days; MATE 7, Activities and Participation, Care and Support (indication of level of functioning in relation to health) in the last 30 days; MATE Q1, Craving Scale regarding the last 30 days; MATE Q2, Anxiety, Depression, Stress Scale (indication of comorbid symptom severity) in the last 30 days.

4.5.2 Main results treatment outcomes

4.5.2.1 Self-efficacy to abstain from Alcohol use

A best subset regression analysis showed that motor timing deficits at baseline hold a prognostic value with regard to self-efficacy to abstain from alcohol use ($R^2=.27$). Spatial errors (at ISI 300 m/sec) at baseline were predictive of total change in percentages in self-reported self-efficacy to abstain from alcohol use ($b= -.26$, $t(50) = -2.05$, $p=.04$). Synchronisation errors were also found predictive of change in alcohol self-efficacy scores at discharge. Synchronisation errors (at ISI 400 m/sec) at baseline were predictive of total change in alcohol self-efficacy scores ($b= -.37$, $t(50) = -2.14$, $p=.03$). Inter-Response Intervals (IRI) were also found to be predictive of alcohol self-efficacy to abstain from alcohol use at ISI 500m/sec intervals ($b= -.28$, $t(50) = -2.10$, $p=.04$) and ISI 700m/sec intervals ($b= -.28$, $t(50) = -2.01$, $p=.04$). Although not statistically significant, synchronisation errors and IRI errors at the 1100m/sec interval conditions occurred in 20 and 17 times, respectively, in the top 20 best predictor models.

4.5.2.2 Self-efficacy to abstain from Cocaine use

A best subset regression analysis showed that motor timing deficits at baseline hold prognostic value with regard to self-efficacy to abstain from cocaine use ($R^2=.25$). Spatial errors at 300 m/sec intervals ($b= -.31$, $t(50) = 2.62$, $p=.01$) and at 500 m/sec intervals ($b= .36$, $t(50) = 2.69$, $p<.01$) at baseline were predictive of total change in percentages in self-reported self-efficacy to abstain from cocaine. Contact times at 300 m/sec intervals were also found to be predictive of total change in cocaine self-efficacy ($b= .31$, $t(50) = -2.62$, $p=.01$). Although not significant, synchronisation errors at 300m/sec interval condition occurred in 17 of the top 20 best predictor models.

4.5.2.3 Prognostic value of motor timing in relapse prediction

Of the 74 participants, 44 were interviewed at 12 months post-discharge, with 33 participants lost to follow up. Data from 36 participants with the least missing data were used for these analyses. Of these 36, 6 relapsed while all other participants remained abstinent of drug and alcohol use post-discharge. Due to the small sample, and limited power, we were unable to analyse and report on predictors of relapse.

4.6 Discussion

Motor timing alone predicted 27 percent of the variance in total score change on the Alcohol Self-Efficacy Scale. Specifically, SE, Asynchrony errors and IRI errors at baseline predicted self-efficacy at treatment completion. With regard to prognostic value of motor timing in change in cocaine self-efficacy scores at treatment completion, we found 25 percent variance explained. SE and CT were predictive at very fast tempi (300m/sec). In the small follow up sample, SE at baseline seemed to indicate a trend towards predicting relapse at 12 months. The results of this investigation show us that motor timing holds prognostic value with regard to treatment outcomes. Motor timing predictors for relapse remain unclear. These findings require investigation going forward to provide novel insights on the prognostic value of treatment outcomes in SUD. To our knowledge, it is the first study of its kind, so we encourage other future research to further explore the prognostic value of motor timing performances, especially synchronisation abilities.

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5 Motor Timing Outcome differences between Patients with Alcohol- and/or Cocaine Use Dependence in a Rehabilitation Program

Chapter 5 presents the findings from the secondary aims of this study. The study assessed for differences in motor timing performances in Cocaine and/or Alcohol groups at baseline and at discharge, examining for possible recovery of motor timing (between visits 1 and 2). The chapter has been presented here in the format of a journal article, as this section will be submitted for publication.

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Author's Contributions

SY Young: Drafting and revising of the manuscript. M Kidd: Assisted with the analyses of the data. Professor S Seedat assisted with the analyses of the data and critically revised the protocol.

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5.1 Abstract

Introduction: Substance Use Disorders (SUD) lead to brain structural and functional deficits associated with cognitive and social functioning deficits in affected individuals and impacts on their treatment outcomes. The lack of behavioural autonomy is underpinned by direct reward, high impulsivity and difficulties in planning behaviour. The motor cortex- as part of a neural mechanism accounting for action and intention- plays a fundamental role in complex cognition, motor performance and coordination. **Methods:** The study sample consisted of 74 abstinent patients, aged 18-60, diagnosed with alcohol and/or cocaine dependence. Participants were all inpatients at a private treatment programme for drug/alcohol dependence at the treatment clinic in Somerset West, South Africa. The main question addressed was whether motor timing abilities would improve over time (as a function of recovery) in patients admitted to a rehabilitation programme for SUD. **Results:** Timing abilities in SUD improved with prolonged abstinence. Timing in decision making (cognitive control) did not improve over time. Rhythmic abilities and synchronisation with external events, as well as spatial abilities, improved with prolonged abstinence. **Conclusions:** This study shows for the first time that motor timing abilities recover significantly with prolonged abstinence. Improvements were observed in movement initiation and execution, and interval timing (both in time and in space). Not all motor timing abilities, and not every type of SUD, recovered equally, thereby suggesting that different substances may affect the brain differently with regard to timing abilities. These findings suggest that motor timing should be investigated further in clinical settings.

5.2 Background

Drug abuse is one of the main causes of death among young people in Europe (*Europees Drugs- rapport*, 2014). Death due to an overdose, or death resulting from a degree of drug-related violence, suicide, illness and accidents shows a mortality rate of 1-2 percent, a figure that is ten to twenty times higher than the expected mortality rate in young people (*Europees Drugs- rapport*, 2014). Furthermore, there are an estimated 1.2 million people in treatment for Substance Use Disorder (SUD) in Europe (EMCDDA home page | www.emcdda.europa.eu, n.d.). These figures are not only worrisome but make the prevention of drug use, the supply of quality interventions in addiction care, and evidence-based research on their effectiveness, necessary. On a functional level, chronic use of substances impacts on judgement, increases craving, impairs salience for natural rewards, increases compulsion, decreases judgement, motivation, and self-control, and promotes relapse (Volkow & Fowler, 2000; Volkow, Fowler, Wang, & Goldstein, 2002; Volkow, Fowler, & Wang, 2004).

A substantial body of research points to aetiological, evolutionary, developmental, and genetic forces in SUD (Goldstein et al., 2009; Goldstein & Volkow, 2011; Kalivas et al., 2005; Wise, 2000); however, the precise way in which these pathogenic mechanisms underlie the deficits in SUDs remains largely unknown (Volkow et al., 2008). There is consensus that SUD is associated with dopaminergic dysregulation, dysfunction of fronto-cortical (orbitofrontal cortex and nucleus accumbens) and memory circuits (amygdala, hippocampus, thalamus), and is further characterised by a marked disruption in brain reward mechanisms.

5.2.1 Motor timing and SUD

SUD leads to brain function deficits associated with cognitive and social functioning deficits, their treatment outcome, and the risk of relapse (Bates, Buckman, et al., 2013; Bell, Garavan, & Foxe, 2014; Goldstein et al., 2004; Strowig, 2000; Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000; Verdejo-García et al., 2012). It is not that substance abusers do not

understand that the disadvantages of continued use outweigh the advantages; rather, they have difficulty resisting the impulses to continue (Wiers & Stacy, 2006). This substance dependence-specific lack of behavioural autonomy cycle is primarily guided by direct reward, high impulsivity, difficulty in foreseeing the consequences of actions, and difficulties in planning behaviour (Bechara, Noel, & Crone, 2006; Goldstein et al., 2009; Goldstein & Volkow, 2011; Hyman, Malenka, & Nestler, 2006; Kalivas & Volkow, 2005; Koob & Le Moal, 2005; Leeman & Potenza, 2012). Research suggests that the motor cortex- as part of a neural mechanism accounting for action and intention- plays a fundamental role in complex cognition, motor performance and coordination (Gallese, Rochat, Cossu, & Sinigaglia, 2009). In the field of psychopathology, research on perception, action, its temporal dimension, and the neural mechanisms underlying the brain's ability to measure time, is attracting interest (Matthews & Meck, 2014; Raghavan, Prevosto, & Sommer, 2016). Studies have shown that motor timing, specifically in the sub-second range, is affected in psychopathological conditions, with disruption in functioning of the PFC, hippocampus, basal ganglia and cerebellum. Additionally, modifications to the neural systems that support interval timing have been shown to contribute to cognitive dysfunction (Brighouse et al., 2013; Buhusi & Meck, 2005; Comte et al., 2014; De Corte & Matell, 2016; Gallese et al., 2009; Lewis & Miall, 2003; Soares et al., 2016). Motor timing, which is defined as a component of temporal processing, regulates the generation of timed motor responses, and is fundamental to our ability to coordinate movements according to time related structures (Mauk & Buonomano, 2004).

Motor timing underpins motor representation of time intervals and is also necessary for sensory motor synchronisation (Repp & Su, 2013), self-initiated movement sequences (Bortoletto et al., 2011), and cognitive control (Raghavan et al., 2016).

The underlying neural systems that coordinate timed behaviours are regulated by the brain's dopamine (DA) system and its target neural substrates (Striatum and PFC) (Brighouse et al., 2013; Soares et al., 2016; Wittmann & Paulus, 2008). Novel research, using rats, has shown that the direct pharmacological suppression of DA neurons decreases behavioural

sensitivity to time and affects the encoding of time variability by DA neurons. The researchers concluded that time estimations and judgements are controlled by DA neurons in the midbrain (Soares et al., 2016). Deficits in timing-related cognitive functioning are shared by a range of otherwise distinct psychopathologies associated with DA dysfunction, including Parkinson's Disease, Schizophrenia and SUD (Avanzino et al., 2016, 2013; Berlin & Rolls, 2004; Coull et al., 2011; Delevoeye-Turrell et al., 2007, 2012; Drew et al., n.d.; Moreira et al., 2016; Rao et al., 2009; Volkow et al., 2004).

5.2.2 SUD treatment outcomes

The precise mechanisms by which chronic substance use and abuse change brain functioning and how the clinical correlates of deficits are related to it have not been delineated (Domínguez-Salas, Díaz-Batanero, Lozano-Rojas, & Verdejo-García, 2016; Moselhy et al., 2001). There is also a lack of consensus with regard to which cognitive functions are most severely affected by SUD and the time taken to reach optimal cognitive recovery (Bates, Bowden, et al., 2013; Bates et al., 2002; Stavro et al., 2013; Walvoort, Wester, & Egger, 2013). Alcohol Use Disorder (AUD) and Cocaine Use Disorder (CUD) are most consistently associated with cognitive-executive impairments (Potvin, Stavro, Rizkallah, & Pelletier, 2014; Stavro et al., 2013). With regard to neuropsychological deficits and treatment outcomes, a recent review found that cognitive control and general cognition had the strongest associations with each other. However, again, due to the large variability between studies definite conclusion could not be drawn (Domínguez-Salas et al., 2016). Both general cognition and temporal processing are believed to play a crucial role in higher order cognitive functions, (Domínguez-Salas et al., 2016; Wittmann et al., 2007). These cognitive abilities are needed to successfully engage and comprehend most psychotherapeutic interventions available at present for SUD (Aharonovich et al., 2006; Bates et al., 2002). With regard to recovery, cognitive deficits present at 1 month have been shown to persist at 1 year (Stavro et al., 2013), which is a period when individuals are often admitted into treatment (Stavro et al., 2013).

A recent study investigating general motor proficiency across several psychiatric disorders (including substance abuse) in groups of adolescents ($n=144$) compared to normally ($n=87$) developing peers indicated that the clinical group performed significantly worse in comparison to the healthy peer control group on all motor proficiency scales. These results were robust regardless of diagnosis, suggesting that objective motor assessment should form part of routine clinical practice (Van Damme, Fransen, Simons, van West, & Sabbe, 2015). To our knowledge, there are no temporal processing studies which specifically focus on motor timing aspects and possible deficits in AUD and/or CUD populations.

Few studies are available on timing deficits in SUD other than AUD and CUD indicate that these individuals do experience motor timing deficits (Wittmann et al. 2007; Moreira et al. 2016). There are a few studies that focus on the immediate effects of Alcohol or Cocaine use on motor timing. One study has shown that alcohol administration significantly increases motor timing variability on finger tapping tasks; a comparison between a grip force task and finger tapping task showed that motor timing, but not motor coordination, was variable to the effects of alcohol (Terry, 2008). Another study comparing the effects of Cocaine and Ketamine on trimming behaviour in rats indicated that ketamine produced no change in timing abilities whereas Cocaine use did (Cheng, Mac Donald & Meck, 2006).

To our knowledge, no study has compared the possible recovery of motor timing aspects of temporal processing following sustained abstinence in AUD and/or CUD. The main aim was to assess recovery in motor timing abilities. Secondary aims were to examine individual differences between Cocaine and/or Alcohol Use Disorder groups. Specifically, we compared motor reactivity, inhibitory control and synchronisation abilities at baseline and discharge (week 1 and 8) in three groups (AUD and/or CUD). The main question we asked was whether motor timing abilities would improve over time (as a function of recovery) in patients admitted to a rehabilitation programme for SUD. We hypothesized that at 8 weeks, the ability to plan and coordinate movements would improve (post-treatment) expressed through; (i) smaller movement times at increased environmental difficulties (recovery of timed

motor coordination/planning abilities, condition 2 & 3 on the Motor reaction task [1]); and (ii) increased cognitive control (higher inhibitory capacities expressed through lower reaction times after a Nogo Target and after a Nogo error Target) on a decision making task (Go-nogo task [task 3]). We also expected improvement in synchronisation abilities expressed through; (i) lower synchronisation errors (ii) fewer inter-response interval errors, (iii) lower contact times and (iv) fewer spatial errors [Spatial-tapping task 2]).

5.3 Methods

5.3.1 Sample

Participants of this study were all inpatients of a private drug/alcohol treatment clinic situated in Somerset West, South Africa. The study sample consisted of 72 abstinent patients, aged 18-60, diagnosed with alcohol and/or cocaine dependence. Patients with a primary diagnosis of alcohol and/or cocaine dependence, who were detoxified, were included. Patients who met criteria for abuse (lifetime or current) of other substances were included, provided that these were not their primary drugs of use/abuse. Patients who met criteria for dependence for any substance other than cocaine/alcohol were excluded. For the alcohol group, patients were excluded if they had a current or past history of dependence on cocaine. For the cocaine group, patients with a current or past history of alcohol dependence were excluded.

5.3.2 Procedures

This study formed part of a larger study (Young et al., 2016). Participants were all inpatients at a private treatment programme for drug/alcohol dependence at the treatment clinic in Somerset West, South Africa. The clinic offers treatment to individuals - mainly of Dutch nationality (the main patient referral company is situated in the Netherlands). The clinic offers a group therapies, individual counselling, written work and a psycho-educational lecture series. All participants work with an individual therapist who will guide them through the

process. The treatment program formed part of the standard of care for all participants. A full medical examination was conducted on every patient at the clinic (toxicology + biochemistry reports and physical examination by the residential psychiatric nursing staff). Participants were tested at three points in time: (i) within 72 hours of the start of the treatment programme, (ii) after completion of the treatment programme at eight weeks (measure of treatment response), and (iii) at a 12-month follow-up session (measure of relapse). Only session 1 and 2 data was used for this study. Designated counsellors at the clinic enquired from patients about their potential interest in study participation. Only participants who gave written consent and who were eligible on screening were invited for a first research visit. After written consent was obtained, the Measurements in the Addictions for Triage and Evaluation.2 (MATE.2.10) (Schippers et al., 2010), a semi-structured diagnostic interview (MINI) (Lecrubier et al., 1997), and a socio-demographic questionnaire was administered.

Two study visits were conducted at the clinic. Each of these visits entailed filling out self-report questionnaires and experimental motor task testing. All assessments were conducted in a structured manner by either the PI, or a trained research assistant. One research assistant was appointed for a period of 2 years. For quality control, all questionnaire and task performance scores, including data entry, were cross checked by both the PI and the research assistant. For the administration of all assessments, standard Operating Procedures (SOPs) were followed. Task instructions were read out in the same way to each participant (for the SOPs and instructions that were read out for the neuropsychological testing, see appendix A; for Motor task testing, see appendix B). The same order of assessment was used for each visit and for each participant.

To reduce temporal perception variability (Matthews & Meck, 2014) in our experimental context, all assessments were carried out in the same research space, in the same order following a structured standard operational procedures with read out task instructions. After the first visit, an appointment for a second assessment was made. Both assessments were undertaken within 72 hours of initiation of the treatment program and repeated at the end of

the eight week (last 72 hours). The participants were followed up at 12 months as part of the larger study.

5.3.3 Measures

Gender, age, handedness, ethnicity, education, family history of substance dependence, previous admissions/counselling/therapy history, drug or alcohol usage (period of abstinence, physical complaints and craving), level of depression, self-efficacy to abstain from substance use, comorbid disorders (including comorbid symptoms severity), impulsivity, quality of life, and the estimated level of intelligence were assessed with the following: a self-administered demographic questionnaire, patients medical files (intake and discharge reports), the Edinburgh Handedness Questionnaire (EHQ) (Büsch et al., 2010), the *Nederlandse Leestest voor Volwassenen* (NLV) (Schmand, Lindeboom, & Harskamp, 1992), The MATE.2.10 Outcomes Measurement (Schippers et al., 2010), Mini International Neuropsychiatric Interview version 5 (MINI 5) (Lecrubier et al., 1997), The Alcohol Use Disorders Identification Test (AUDIT) (Lundin et al., 2015), and Drug Use Disorders Identification Test (DUDIT), (Hildebrand, 2015) The Alcohol Abstinence Self-Efficacy Scale (AASE) AND The Cocaine Abstinence Self-Efficacy Scale (DiClemente et al., 1994) and the Beck Depression Inventory (BDI) (Beck et al., 1988).

5.3.4 Temporal processing: Action-Based Timing Tasks

The motor tasks consisted of a series of reaction-prediction visuo-motor pointing tasks to measure different aspects of motor timing (motor sequencing, synchronisation, and inhibition). The sequential pointing tasks were all designed by Professor Y. Delevoeye-Turrell and her team at the University of Lille, France. These tasks have been used in previous research but not SUD research, nor prognostic research of any kind previously (Delevoeye-Turrell et al., 2007, 2012; Dione et al., 2005; Dione et al., 2013; Dione & Delevoeye-Turrell, 2015). For testing, participants were seated in front of a tactile screen (Elo Touch) of 53cm by 36cm by 30 cm which was placed close to the participants' midline in order to avoid muscle

fatigue from the repetitive pointing movements. Visual and auditory signals were controlled via a PC with coded software in C++. For a detailed overview of these tasks, please see the protocol publication (Young et al., 2016)

5.3.4.1 Reactivity: the motor reaction task

The subjective representation of time is crucial when the central nervous system plans and then executes an accurately spaced and timed reaction (Avanzino et al., 2013; Bortoletto et al., 2011; Bortoletto & Cunnington, 2010), meaning that an interval between movements less than a second will lead to the complete structure of the sequence being planned before movement execution (Bortoletto et al., 2011). Thus movement initiation and rhythm are processed into an action plan before the movement occurs (Bortoletto & Cunnington, 2010). Motor reactivity abilities were evaluated using a simple finger-pointing task to visual dots presented on the touch screen. Participants are required to lift (action initiation- measured as Reaction Time) and touch (action execution- measured as Movement Time) one dot (condition one,) a series of two (condition 2) or of three dots (condition 3).

The manipulation of the complexity (the number of dots) of the motor sequence thus provides the means to assess the lower order timing mechanism (one target) and higher order mechanisms (2 and 3 dots) through the capacity of participants to structure, organize and plan an action through time and space by ensuring accurate pointing in combination with fast movements. Condition one is designed to measure lower order mechanisms of movement initiation and execution, whereas condition 2 and 3 were designed to measure higher order mechanisms through increased complexity which requires structuring and planning of motor timing. Participants are instructed to start with the index finger of the dominant hand placed on the square starting zone which is situated at the bottom left edge of the screen. As soon as a black dot appears on the screen, the task is to lift of from the central target (square) and touch the target(s) as fast as possible. Three levels of complexity were counterbalanced: one target, two-target or three-target conditions.

5.3.4.2 Synchronisation: The Spatial-tapping task

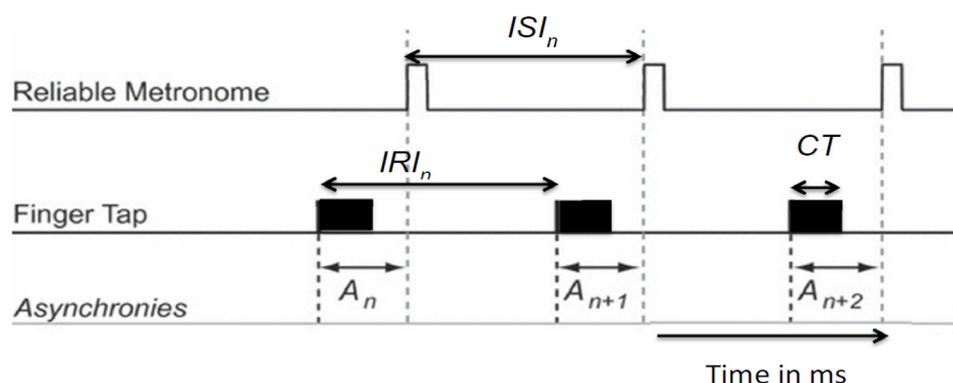
Synchronising movements to external events is an ability that is central to adaptive behaviour. Popular research paradigms for the measurement of motor timing abilities are sensorimotor synchronisation tasks. These tasks entail finger tapping and circle drawing paradigms (Yvonne, Repp, Dione & Repp, 2013), measure the coordination of rhythmic movements with an external rhythm and are frequently used as a way to measure motor timing abilities (for a detailed review on sensory motor synchronisation research, see Repp, 2013).

With this task, we aimed to evaluate how well self-initiated actions to external stimuli, present in the environment, are timed (synchronised) using a Spatial-tapping task (Dione et al., 2013). This task measures pointing accuracy in time and space as well as error in fluency and accuracy. On the tactile screen display are six black dots of 100 mm apart in a circle. The task is to touch each target, one after the other, starting from the bottom right target, and moving counter-clockwise using the right index finger (fist closed). Each condition is constituted of a series of sixty taps of, in total, 5 trials. The total duration of the task is approximately 10 minutes.

There are two experimental conditions: the tempo of the external rhythm is fixed in terms of inter stimulus interval (ISI) and is considered an important independent variable in timing research. In each trial, participants were presented with an auditory rhythm that must be used to pace their actions (ISI= 1100m/sec; 700m/sec, 500m/sec, and 300m/sec). After listening to the tones for 5.5s, participants start tapping for a total trial duration of 35s. Timing performances on this task were measured through Inter-response interval errors (IRI error) and Synchronisation errors (Asynchrony). The IRI was measured as the time intervals between the start of two successive taps. The IRI error was then computed as the percentage of absolute difference between each IRI and the reference inter-onset interval (ISI) of a given trial.

Synchronisation errors (asynchrony) were measured through the difference between onset of a tap and the time of onset in the external rhythm. See figure 5.1 for an overview of how IRI errors, CT, and Synchronisation errors were measured. Spatial performances were measured through the measurement of endpoint distributions of pointing actions and were plotted as a function of each visual target position. The mean spatial error (SE) of these spatial ellipses were used as an indication of spatial performances (Dione & Delevoeye-Turrell, 2015). The control of pauses was measured through contact time (CT) and defined as the time of finger contact with the touch screen. This measure (in m/sec) was used as an indicator of the amount of voluntary pauses in the gesture.

Figure 5-1 Visual overview of Inter response interval, Inter Stimulus interval, Asynchrony and Contact



Note: IRI - Inter response interval, ISI - Inter Stimulus interval, A - Asynchrony, CT, Contact Time

5.3.4.1 Decision-making: The Go-nogo task

In order to achieve positive outcomes in the future and function effectively, urges for immediate gratification have to be postponed, and goal directed behaviour has to be given preference (Zimbardo & Boyd, 1999). To do this effectively and efficiently, inhibitory capacity is necessary. Flexible goal-directed behaviour requires an adaptive inhibitory system for selecting contextually relevant information and for organizing and optimizing information processing. A modified version of the Go-nogo paradigm was designed to measure reaction times through

a tactile touch of the touch screen. The starting zone is situated at the bottom left edge of the screen. The target is a white circle with a black letter or one-digit black number, and participants are instructed to act as fast as possible (Go) or to refrain from acting (Nogo), depending in the condition of the task. In the first condition, the task was to tap the target that appears as fast as possible (100% Go).

In the following blocks, participants are instructed to react and tap the target as fast as possible, but only if the target is a letter (50 % Go). If the target is a number, they are to refrain from reacting. Numbers and letters were presented in semi-random order. The targets were presented for 5s on the screen, with a random phase lag of ± 300 ms in order to avoid anticipatory responses. To assess inhibitory capacity types, the reaction times obtained after a Go Target (of both Go (1) and Nogo (2) conditions), after a Nogo Target, and after a Nogo Target error (i.e. touched the Nogo Target) were used. Cognitive control was measured through decision making (reaction time after Go Targets and Nogo Target) and adaptability (reaction time after a Nogo Target Error)

5.4 Data Analysis

Possible confounding group characteristics were compared using *Analyses of Variance* (ANOVA). These variables can be found in table 1 under 'group comparisons'. A three-way repeated measures analyses of variance (RMANOVA) was conducted with Group, Session and Condition as factors. In the Motor Reaction Task, motor sequencing was examined on three levels of complexity, which were counter-balanced: 1 Target, 2 Target or 3 Target Condition. In all Conditions, we calculated the means and standard deviations for Reaction Time (time between target presentation and finger lift off of the square square) and Movement Time (time between target presentation and finger lift off of the square square) to the first target only for each individual (for every Condition). In the Go-nogo task, we measured reaction times as a function of trail Type.

To assess cognitive control ability types, mean reaction times were calculated for the Go trials when the trial followed a Go Target (React/React), after a Nogo Target (Refrain/React) and after a Nogo Target Error (Adapt). In the Spatial-tapping task, Sensory Motor Synchronisation was measured on different levels (timing and spacing). The IRI error was computed as the percentage of absolute difference between each IRI and the reference inter-stimulus interval (ISI) of a given trial. Synchronisation errors (asynchrony) were calculated from the difference between onset of a tap and the time of onset in the external rhythm. Both IRI Errors and Asynchrony were used as an indicator of timing (synchronisation) capacity. The endpoint distributions of the pointing actions were plotted as a function of each visual target position. Through vector calculations, spatial ellipses were then calculated. The mean Spatial Error (SE) of the spatial ellipses was measured in mm² (Dione & Delevoeye-Turrell, 2015). Contact time (CT) was measured in milliseconds.

5.5 Results

5.5.1 Sample

5.5.1.1 Demographics

All participants included in this study completed treatment. All participants were right handed ($n=59$), 80 percent were male, and the mean age was 36.6 years old ($SD= 10.5$, $mode= 27$, range 19-60). Forty-two participants (59%) were employed whilst 27 participants (36.5 %) were receiving unemployment benefits. Half of the participants were single, 13 participants (20%) were divorced, and 28 participants (40%) had children.

5.5.1.2 Clinical Characteristics

Patients with comorbid disorders at baseline were excluded from entry into the study; however, at discharge (8 weeks), some participants had been diagnosed with comorbid disorders ($n=10$, 15% Axis 1 Psychiatric disorder; $n= 15$, 20% Axis 2 Personality Disorder; $n=5$, 7% both Axis 1 and 2). Previous outpatient treatment had been attempted by $n= 38$

(51.4%), $n= 23$ (31%) had received psychotherapy, 12 participants (16.2%) had previously been admitted to psychiatric inpatient care (non SUD- majority due to a failed suicide attempt), and for 21 participants (29%) of the participants this was the second (or more) attempted inpatient rehabilitation. On admission, 23 participants (31%) had a positive alcohol test (through Breathalyzer examination) and 38 participants (54%) had a positive drug test (Cocaine $n=25$ (33%), Benzodiazepine $n=8$ (10.8%), Cannabis $n=5$ (6.8%), and Amphetamine $n=1$ (1.4%). Drug use other than Cocaine and/or Alcohol was minimal, with 9 percent using Methylenedioxymethamphetamine, other stimulants (e.g. Speed, Methamphetamine 15 percent), Sedatives (prescription 12 percent) in the 30 days before admission to treatment.

For 22 participants (30%), detoxification prior to admission to the clinic was necessary. Comorbid psychiatric symptoms were below clinical threshold on the Anxiety, Depression and Stress scale (MATE Q2 total score of < 60) ($M= 41.8$, $SD= 25.2$, mode=12). Craving symptoms were minimal at baseline (MATE Q1 total scores of <12) ($M= 7.5$, $SD= 3.9$). A detailed overview of the described clinical measures can be found in Table 5.1

	N=74		Alcohol		Cocaine		Alcohol/Cocaine		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
IQ	112	9.89	110	10.8	109	9.8			ns
Alcohol Use last 30 days	18.5	10.1	4	5.3	16.6	8.3			
Alcohol quantity used last 30 days (units)	15.2	9.56	5.7	7.4	16.4	15.6			
Cocaine Use last 30 days	1	.8	15.3	10.6	10.8	9.7			
Cocaine quantity used last 30 days (grams)	.5	.04	3.2	3.4	1.3	1.4			
AUDIT	25.3	8.9	8.2	5	24.6	7.5			
DUDIT	7	8.1	31.5	7.6	28.56	8.8			
Quality of Life	16	7.1	21.4	6.3	17.41	9			ns
Cognitive Impulsivity*	84.1	11.6	93.6	12.6	98.4	13.9			<i>p</i> <.01
Duration of Use**	24.2	11.9	12.4	7.6	15.2	8.3			<i>p</i> <.01
Age of first Use	20.5	9.3	20.9	5.5	17.32	4.1			ns
Abstinence in days	16	14.1	14.6	12.1	14.2	10.43			ns
GAF score at admission	52.83	6.9	51.5	11.7	52.5	7.5			ns
MATE 5	12.2	6.8	9.1	8.4	11.6	7.7			ns
MATE Q1	6.7	3.3	7.9	4.2	7.8	4.2			ns
MATE Q2	19.1	12.9	21	11.7	22.3	13.5			ns

Note: Results of separate groups; IQ: *Nederlandse Leestest voor Volwassenen*, indication of intelligence, AUDIT: Alcohol Use Disorder Identification Test, DUDIT: Drug Use Disorder Identification Test; Quality of Life, Sheehan Disability Scale (SDS), Impulsivity, (BIS) Behavioural Inhibition Scale; GAF: Global Assessment of Functioning. MATE 5; Measurements in the Addictions for Triage and Evaluation, Physical Complaints/health related symptoms in the last 30 days; MATE Q1, Measurements in the Addictions for Triage and Evaluation, Craving Scale regarding the last 30 days; MATE Q2, Measurements in the Addictions for Triage and Evaluation, Anxiety, Depression, Stress Scale last 30 days.

*Post hoc analyses revealed that the Alcohol group was significantly less impulsive compared to both the Cocaine and Alcohol/Cocaine groups, the Cocaine and Alcohol/Cocaine groups did not differ significantly

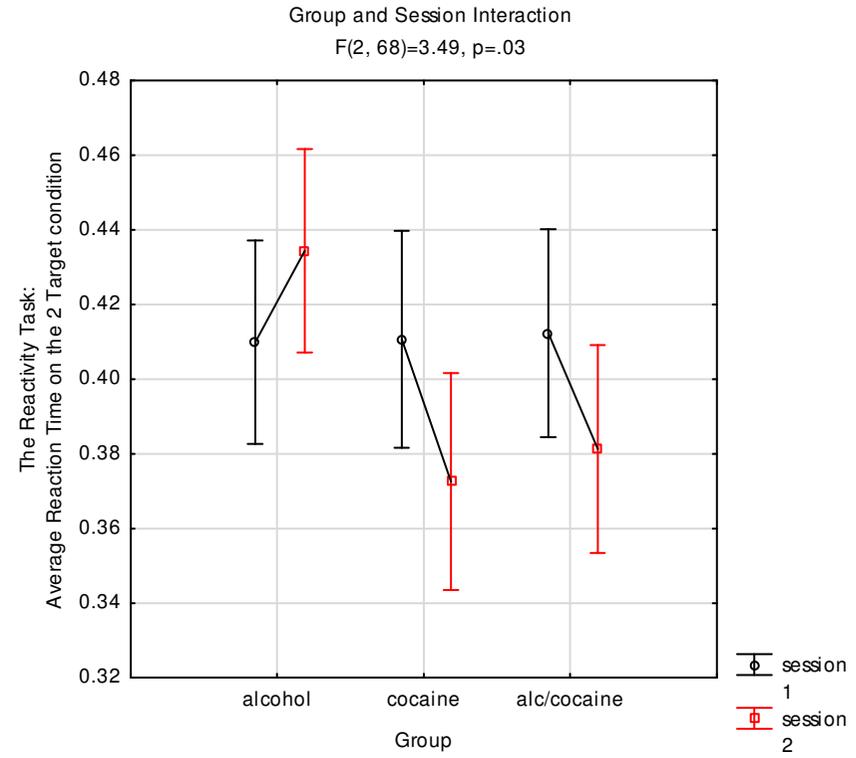
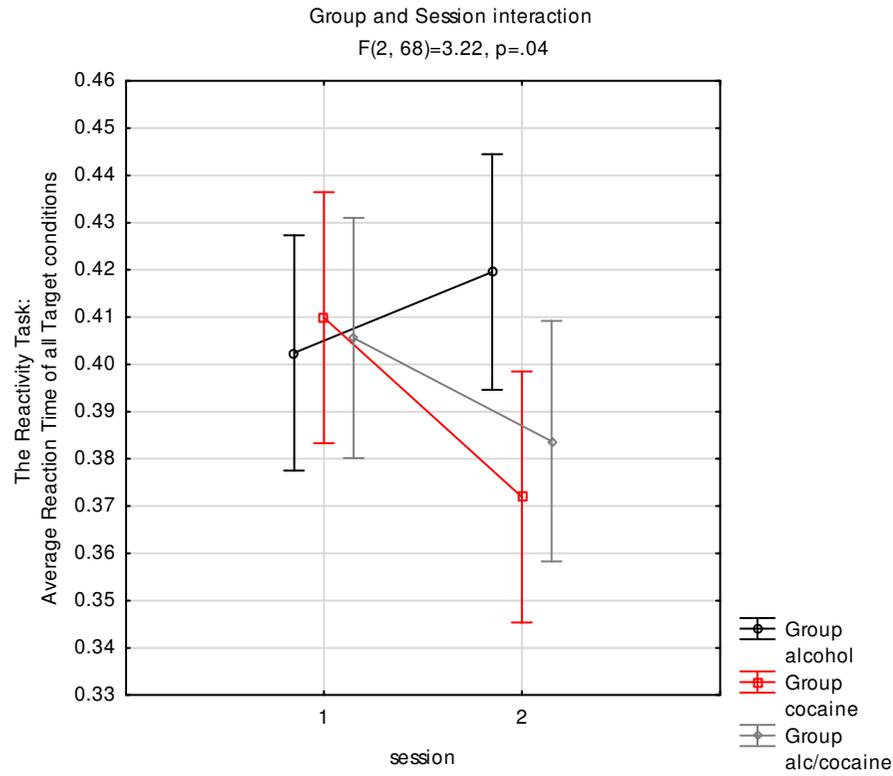
** The Alcohol group had a significantly longer duration of use compared to the Cocaine and Alcohol/Cocaine groups. The Cocaine and Alcohol/Cocaine groups did not differ significantly. Since age of first use did not differ significantly between groups, we did not control for this in further analyses.

5.5.2 Reactivity; the Motor Reaction Task

5.5.2.1 Movement initiation; Reaction Time

No main effect was found for Session on Reaction Time. Mean Reaction Time (reaction times of all conditions averaged) did decrease from session one ($M=.40$, $Std\ error=.007$, $CI=.39-.42$) to session two ($M=.39$, $Std\ error=.007$, $CI=.39-.40$). No main effect for Condition was found. An interaction effect of Group and Session was found ($F(2.68)=3.22$, $p=.04$). Post hoc analyses revealed that the Cocaine group had slower reaction times pre-treatment ($M=.40$, $Std\ error=.01$, $CI=.37-.40$) compared to post-treatment ($M=.37$, $Std\ error=.01$, $p=.02$, see figure 5.2a). Leaving Condition out of the RMANOVA and re-analysing the results yielded interesting findings. No Session effect, nor Group and Session interaction effects on condition 1, and Condition 3 were found; however, in Condition 2, a significant Session and Group interaction effect was found ($F(2.68)=3.49$, $p=.03$). Post hoc analyses revealed that the CUD differed significantly pre- and post- treatment ($p=.03$) whilst the AUD and/or CUD group differences were found insignificant (see Figure 5.2b).

Figure 5-2 Average reaction time of all targets between sessions (a, left) and average reaction time of the 2 target condition between sessions (b, right)



5.5.2.2 Movement execution: Movement Time

No main effect was found for Session Movement Time (all Condition reaction times combined and averaged) did decrease between session one ($M = .35$, $Std\ error = .009$, $CI = .33; .36$) and session two ($M = .34$, $Std\ error = .009$, $CI = .32; .36$). A main effect for Condition was found ($F = (2.136) = 113$, $p < .01$). The 1 Target Condition differed significantly from the 2 Target Condition ($Mean\ difference = .06$, $Std\ error = .01$, $p < .01$, $CI = .05; .07$) and the 3 Target Condition ($Mean\ difference = .07$, $Std\ error = .01$, $p < .01$, $CI = .06; .08$). No Group and Session interaction effect was found.

5.5.3 Decision making: The Go-nogo task

No significant main effects or interaction effects were found for Session and/or Group on reaction times after a Go Target, a Nogo Target (decision making), or after a Nogo Error was made (adaptability).

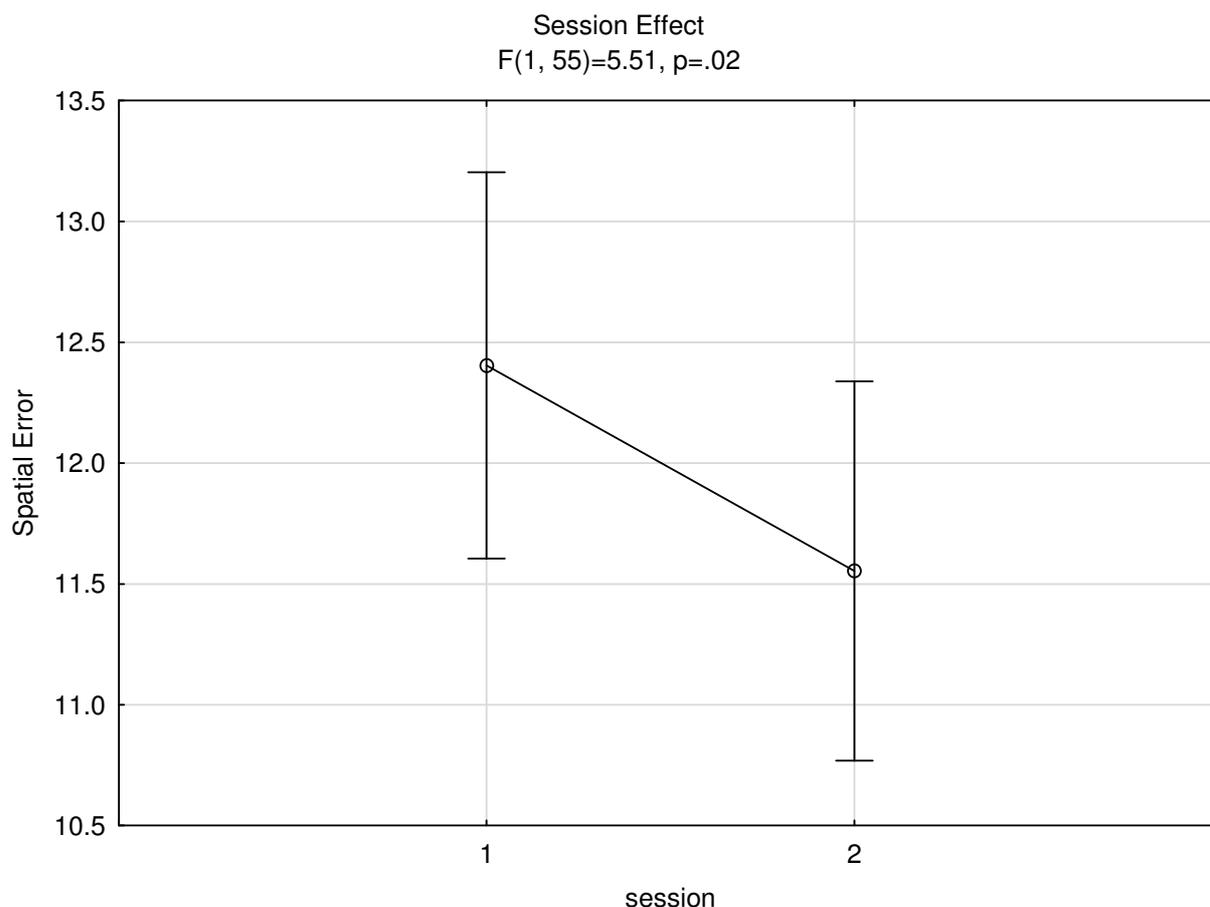
5.5.4 Synchronisation: The Spatial-tapping task

Timing performances in time and space were examined through different interval timing task conditions. In the spontaneous rhythm condition, only spatial abilities were assessed.

5.5.4.1 Spontaneous rhythm- Contact Time and Spatial Error

No main effect was found for session on CT in the spontaneous rhythm condition. With regard to SE, a main effect was found for Session. SE at session one ($m = 12.4$, $SD = .39$, $11.6-13.2$) were less at session two ($M = 11.55$, $SD = .39$, $10.76-12.33$) which was significant ($F(1,55) = 5.50$, $p = .02$). No group and session interaction effect was found for SE and CT. See figure 5.3 for an overview of SE.

Figure 5-3 Average mean Spatial Errors using the participant's spontaneous rhythm

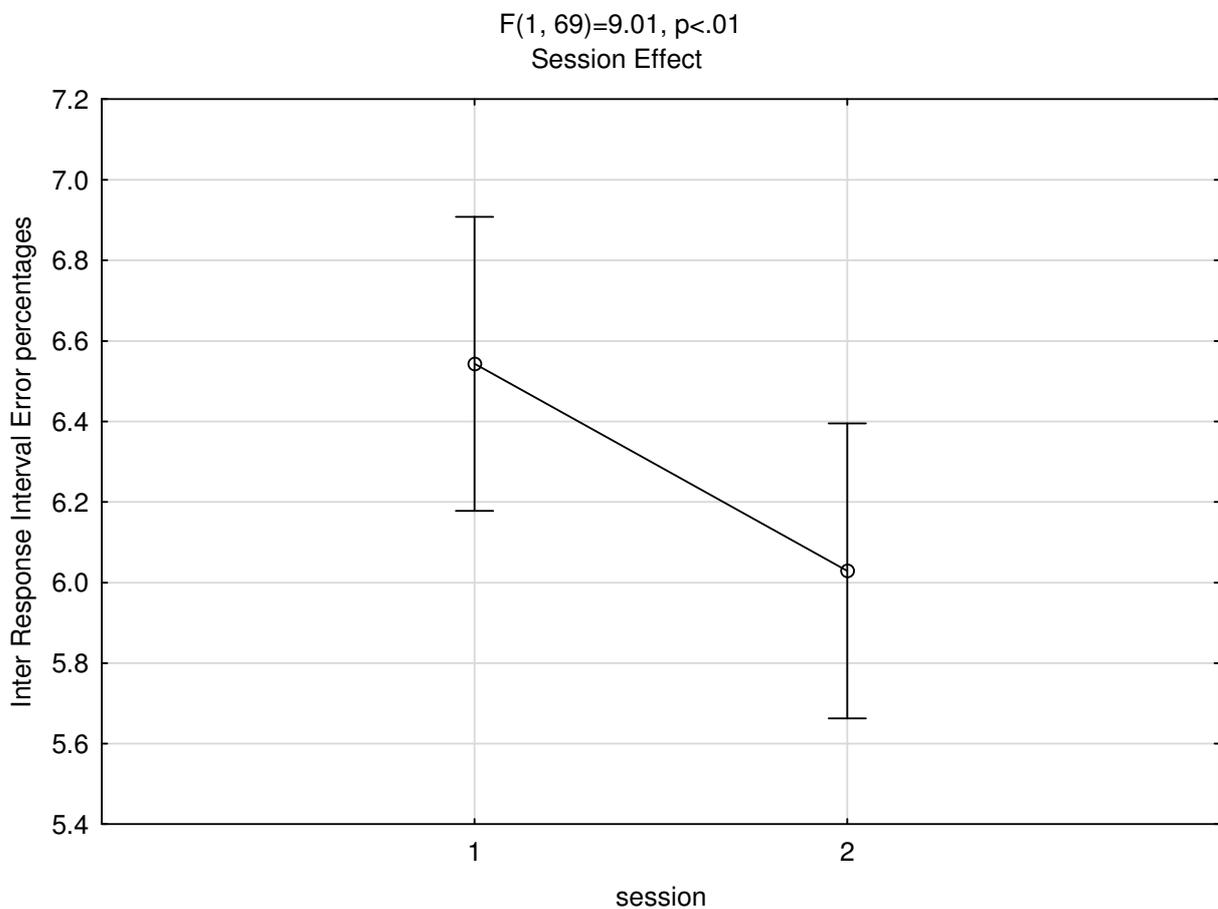


5.5.4.2 Timing abilities during interval timing- inter response interval errors

A main effect was found for ISI ($F(8.359) = 26.74, p < .01$) and IRI Errors. Higher IRI Error percentages were found at faster (compared to slower) ISI. A main effect for Session was found on IRI Errors ($F(1.69) = 9.01, p < .01$, see figure 5.4). The average IRI Errors at session one ($M = 6.54, Std\ error = .18, CI = 6.17; 6.90$) was higher than at session two ($M = 6.02, std\ error = CI = .18, 5.66; 6.39$). Post hoc analyses of ISI session differences revealed that the IRR Error percentages differed significantly between sessions at ISI 300 ($mean\ difference = 1.07, Std\ error = .30, CI = .47; 1.66, p < .01$), 400 ($mean\ difference = 1.02, Std\ error = .30, CI = .42; 1.61, p < .01$), 500 ($mean\ difference = .60, Std\ error = .30, CI = .01; 1.20$) and 1100 ($mean\ difference = .77, Std\ error = .30, CI = .17; 1.37, p < .01$). With regards to group differences

and session differences, post hoc analyses revealed that only the AUD/CUD group improved significantly over time (*Mean difference*=2.01, *Std error*= .52, *CI*= -.98; 3.04, $p<.01$). A trend towards significance was observed in the CUD group (*mean difference*=.93, *Std error*= .54, *CI*= -.13; 2.00, $p=.08$), whereas there was no significant improvement in the AUD group (*Mean difference*=.25, *Std error*= .50, *CI*= -.71; 1.25, $p=.59$)

Figure 5-4 Mean Error percentages on Inter Response Intervals of all participants.

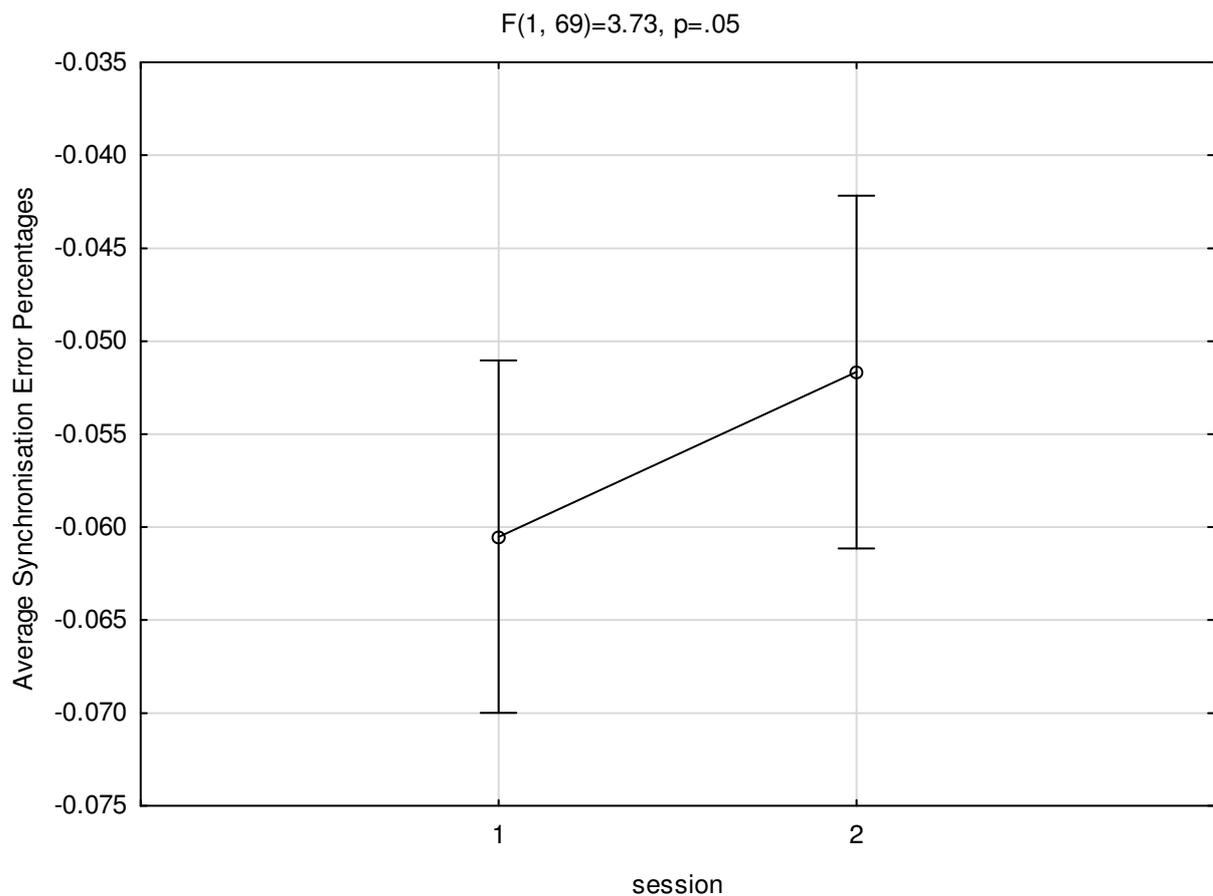


5.5.4.3 Timing abilities during interval timing- Synchronisation errors

A significant main effect was found for ISI ($F(8.35)= 63.45, p<.01$). Synchronisation abilities were poorer at slower ISI. A significant effect for Session was found ($F(1.69) =3.74,$

$p=.05$, see figure 5.5). The Asynchrony percentages pre-treatment ($M=-.06$, $SD=.007$, $CI= -.08; -.05$) improved significantly post-treatment ($M= -.05$, $SD= .004$, $CI= -.06; -.04$). Post hoc analyses revealed that asynchrony percentages pre- and post-treatment differed at ISI 500 ($mean\ difference=-.01$, $Std\ error= .01$, $CI= -.03; .01$, $p<.01$) and ISI700 ($mean\ difference=-.02$, $Std\ error= .01$, $CI= -.03;.01$, $p<.01$). No significant interactions with Group, Session, nor ISI were found. Further analyses revealed that the alcohol group asynchrony percentages differed significantly between sessions ($mean\ difference=-.01$, $Std\ error= .01$, $CI= -.03; .02$, $p<.01$).

Figure 5-5 Mean Error percentages on Synchronisation Error rates for all participants.



5.5.4.4 Spatial abilities on interval timing- contact times and spatial errors

With regard to CTs, a significant main effect was found for ISI ($F(8.359) = 44,84$, $p < .01$). Higher CTs were found at slower ISI. With regard to SEs, a significant main effect was found for ISI ($F(8.359) = 206.0$, $p < .01$). Higher SE were found at faster ISI. No significant main effects or interaction effects were found for Session and/or Group with regard to both CT and SE.

5.6 Discussion

This novel study shows that timing abilities in SUD populations improves with prolonged abstinence. With regard to motor initiation and execution abilities, we found that participants recovered over time. The alcohol group had the lowest overall movement initiation times (Reaction Time) whilst the CUD group had the highest. Only the CUD group significantly improved on movement initiation and execution times, which could indicate a possible recovery in motor planning abilities in this group. Timing in decision making (cognitive control) did not improve over time. Interval timing abilities improved significantly over time. Both rhythmic abilities and synchronisation with external events, as well as spatial abilities, improved with prolonged abstinence. Keeping in tune with a rhythm was harder at faster tempi for all patients at the start of treatment compared to after treatment. However, only the CUD group improved significantly. Additionally, poorer synchronisation abilities were found at treatment start and more so at slower tempi. These performances did improve over time only significantly so for the AUD group. With regard to spatial abilities, improvements were only found for the AUD and CUD groups, but not the AUD/CUD group in SEs. The SE rates for all individuals were lower at discharge compared to admission.

The CT was longer at slower tempi for all participants but did not change over time and was similar for each group. Leading from this, it can be suggested that the improvements observed on both movement initiation and execution and interval timing, in time and in space,

might correspond with the recovery of cognitive abilities in CUD and/or AUD. Further research to examine this possible link is ongoing (Young, in progress). Interestingly, not all motor timing abilities, and not every type of SUD seems to recover the same way. An explanation could be that the brain recovers at different rates and is affected in different ways by different substances. Chronic alcohol abuse is known to damage the cerebellum, which is crucial in motor timing and coordination of fine motor movements (Avanzino et al., 2016, 2013); we may, therefore, be measuring damage caused by chronic abuse of alcohol in these individuals. Previous findings suggest that motor timing holds prognostic value in treatment outcomes in SUD (Young, Kidd & Seedat, in progress). This study now shows for the first time that motor timing abilities recover significantly with prolonged abstinence.

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6 **Motor timing deficits in populations with Substance Use Disorder: a Bimodal Distribution and Evolutionary Neurobiological Model**

Chapter 6 presents the primary aim findings of this study. The paper compared individuals with SUD and Healthy Controls, AND Cocaine and/or Alcohol groups separately on motor timing abilities. Dr van Hoofs' model was applied to the outcomes (e.g. the drive and guidance mechanisms deficits). The chapter has been presented here in the format of a manuscript, as this section will be submitted for publication.

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6.1 Abstract

Introduction: In evolutionary and developmental terms, the ability to anticipate, delay gratification and exercise self-control is acquired over many years of development and is vital not only to survival but also aids us to thrive and evolve. Motor timing, specifically, is fundamental to our ability to coordinate movements and is defined as a component of temporal processing. Modifications to these neural systems contribute to motor timing deficits and pathology. Van Hoof presents a bimodal distribution and evolutionary neurobiological model, which may provide a useful pathogenic framework for the classification of major psychiatric disorders, including SUDs. Major psychiatric disorders (such as SUD) may be understood as manifestations of imbalances between an automatic mode of action (referred to as the Drive Mechanism) and a more cognitive-predictive mode of action (referred to as the Guidance Mechanism, GM). **Methods:** This exploratory study aimed to investigate motor timing deficits in SUD populations alone, and, compared to a Healthy Control (HC) group. Participants were all in-patients ($N=74$) at a private treatment programme at Momentum Mental healthcare South Africa. Two study visits were conducted at the clinic. Each of these visits entailed filling out self-report questionnaires and experimental motor task testing. **Results:** No indication of a faster internal clock rhythm was found amongst patients compared to HC. The capacity to coordinate and plan was also unaffected. We did find lower inhibitory capacities amongst the SUD groups. Inhibition was affected in SUD groups after a Go Target on the Go-nogo task, and after Nogo Errors were made. Additionally, we found a lower capacity to synchronise to in the SUD groups. SUD groups were less able to accurately and fluently synchronise at tempo extremities (fastest and slowest tempi). However, SUD groups outperformed the HC on spatial performances. **Conclusions:** The use of this motor task battery resulted in support of deficits in the GM and the DM as proposed by van Hoof. Patients overall performed more poorly on all other timing abilities, which may have significant implications for future studies. Interestingly, all deficits found only occurred when cognitive load was increased. Inhibitory

timing deficits were only found after a Go Target and after Nogo Target Errors were made, but not after a Nogo Target. A possible explanation could be that errors are perceived as stressful and lead to increased cognitive load and subsequently, a loss of control over inhibition. In fact, all deficits found seem to only occur when cognitive load was increased. Interestingly the SUD groups outperformed the HC on spatial accuracy on the task, whilst they performed significantly worse on timing abilities. Since spatial accuracy heavily relies on visual feedback, performances observed in spatial domains may indicate compulsive traits in these populations. We encourage future researchers to further explore these novel findings.

6.2 Keywords

Motor Timing, Impulsivity, Addiction, Substance Use Disorder, Biomarkers, Action Planning, Cocaine Dependence, Temporal Processing, Inhibition, Impulsivity, Compulsivity, Theoretical frameworks for Substance Use Dependence.

6.3 Background

The capacity to accurately detect and understand the intentions of others, anticipate their upcoming actions, and appropriately adjust one's own behaviour are fundamental to our ability to interact as humans (Gallese et al., 2009). In evolutionary and developmental terms, the ability to anticipate, delay gratification and exercise self-control is acquired over many years of development and is vital not only to survival but also aids us to thrive and evolve (Droit-Volet, 2016; Droit-Volet & Coull, 2015; Gallese et al., 2009; Neufang et al., 2008; Stevens et al., 2007). Accurate cognitive control requires the recruitment of neuro-anatomical and functional components of time perception, and performances on timing tasks have been shown to be sensitive measures of deficits in neural mechanisms and cognitive functioning (Suh, Kolster, Sarkar, McCandliss, & Ghajar, 2006). As such, timing can be seen as a fundamental neuropsychological domain, with a broad influence on cognitive functioning (Foster et al., 2013). It mediates behavioural and cognitive processes as a basic unit of ability (Allman & Meck, 2012), ranging from goal directed behaviour (Alústiza, Radua, Pla, Martin, & Ortuño, 2017) to basic motor coordination (Buonomano, 2007).

Motor timing, specifically, is fundamental to our ability to coordinate movements and is defined as a component of temporal brain processing (Mauk & Buonomano, 2004). Motor timing underpins self-initiated movement sequences (Bortoletto et al., 2011) and sensory motor synchronisation (Repp & Su, 2013) and is inextricably related to motor control (Mauk & Buonomano, 2004; Raghavan et al., 2016). Timed behaviours are coordinated by neural systems regulated by the dopamine (DA) system and its target neural substrates (Striatum and PFC) (Brighouse et al., 2013; Soares et al., 2016; Wittmann & Paulus, 2008). Modifications to these neural systems contribute to (millisecond range) motor timing deficits

and pathology (Brighouse et al., 2013; Buhusi & Meck, 2005; Comte et al., 2014; De Corte & Matell, 2016; Gallese et al., 2009; Lewis & Miall, 2003; Soares et al., 2016). These deficits are shared in a variety of neuro-developmental disorders (Buhusi & Meck, 2005; Gallese et al., 2009; Rubia et al., 1999, 2009; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003) and dopamine function related disorders (such as Parkinson's Disease, Schizophrenia and SUD) (Avanzino et al., 2016, 2013; Berlin & Rolls, 2004; Coull et al., 2011; Delevoeye-Turrell et al., 2007, 2012; Drew et al., 2012.; Moreira et al., 2016; Rao et al., 2009; Volkow et al., 2004) and have been found to be more prevalent in adolescents with a variety of psychopathology, including SUD (Buhusi & Meck, 2005). Research points to aetiological evolutionary, developmental and genetic influences (Goldstein et al., 2009; Goldstein & Volkow, 2011; Kalivas et al., 2005; Wise, 2000); however, the precise way in which implicated pathogenic mechanisms underlie these deficits in the SUDs remains unclear. Despite the potential importance of temporal processing in general psychopathology, and SUD specifically, little attention has been given to the study of motor timing abilities (Coslett et al., 2009; Moreira et al., 2016; Rosenbaum, 2005). In addition, theoretical models that enhance interdisciplinary understanding of SUD are lacking.

6.4 A bimodal distribution and evolutionary neurobiological model for SUD

Van Hoof's bimodal distribution and evolutionary neurobiological model may provide a useful pathogenic framework for the classification of major psychiatric disorders, including SUDs (van Hoof, 2003; Van Hoof, 2002). The model proposes that during phylogenesis and ontogenesis, brain mechanisms - from motoric to limbic areas - are implemented in a repetitive way. The motoric mechanisms necessary for grasping stationary and moving objects evolved and matured to organize cognitive and emotional processes, such as affiliation and intimidation. This organisational process resulted in the capacity to organize intentional behaviour, in that mental representations of intended or goal-action effects are responsible for

the planning and execution of appropriate movements required to achieve a goal (van Hoof, 2003; Van Hoof, 2002).

The description of organisational processes, as provided by the model, is supported by a robust body of research in the fields of human (and animal) neuroscience, developmental psychology and evolutionary psychology (Best & Miller, 2010; Buhusi & Meck, 2005; Coslett et al., 2009; Gallese et al., 2009; Mauk & Buonomano, 2004; Wilson & Cook, 2016), the literature on dual circuitry deficits in SUD (Goldstein & Volkow, 2002; Hyman, Malenka, & Nestler, 2006; Koob & Le Moal, 2005; Volkow et al., 2008). Indeed, the motor cortex plays a crucial role in complex cognitive abilities and forms part of the neural circuitry that accounts for action and intentions, thus providing a foundation upon which social abilities can be built (Gallese et al., 2009). Major psychiatric disorders (e.g., schizophrenia and SUD) may be understood as manifestations of imbalances between an automatic mode of action (referred to as the Drive Mechanism) and a more cognitive-predictive mode of action (referred to as the Guidance Mechanism, GM).

The DM is based upon the compilation of stimulus-response rules specifying the motor routines that action-relevant objects habitually require (sensorimotor learning) and is thought to be controlled by a ventral circuit that includes the parietal cortex, the ventral premotor cortex and the basal ganglia. The GM is a cognitive-predictive mode of action, based on a compilation of action-effect rules specifying the actions and effects produced. This is a dorsal circuit which is mediated by front striatal circuits. The GM includes the dorsolateral prefrontal cortex, anterior cingulate, SMA (medial premotor cortex) and the cerebellum. The literature on temporal processing and motor timing, specifically, supports this bimodal distribution of motor and cognitive coordination (Buhusi & Meck, 2005; Grondin, 2010; Herwig et al., 2007; Hommel, 2003; Iversen & Balasubramaniam, 2016; Kalivas et al., 2005; Lewis & Miall, 2003; Logan & Cowan, 1984; Prinz, 1997; Wittmann et al., 2011). This exploratory study aimed to further investigate motor timing deficits in SUD populations compared with an age-, gender-, IQ-, and handedness- and matched Healthy Control (HC) group. These deficits could

potentially reflect an imbalance between the DM and GM (i.e., comparatively high activity of the DM and a comparatively low activity of the GM).

We investigated motor timing deficits in SUD populations compared to a HC to indirectly test the model proposed by Van Hoof (2002, 2003). Deficits in motor timing could reflect an imbalance between the DM and GM (a comparatively high activity of the DM and a comparatively low activity of the GM). We assessed for motor planning and coordination, decision making and synchronisation abilities. We expected decision making to be expressed as the measurable attempt to inhibit making error, or adapting after an error has been made. This would be expressed as faster reaction times after a Go Target compared to reaction times after a Nogo Target and a Nogo Target Error, indicating cognitive control over behaviour. With regards to the DM, we expected to find (i) higher internal clock rate (higher spontaneous rhythms on the Spatial-tapping task [Task 2]); (ii) lower motor coordination and planning (higher reaction times and lower movement times on the Motor reactivity task [Task 1]) and; (iii) lower inhibitory capacities (higher reaction times on the Go stimuli in the Nogo trail and more errors on the Nogo stimuli in the Nogo trail [Task 3]) in SUD individuals compared to HC. With regards to the GM, we expected to find lower synchronisation abilities (the spatial-tapping task trails that are at higher tempi [Task 2]) in addicted individuals compared to HC. Furthermore, we expected that within the SUD group we would find (i) a comparatively lower inhibitory capacity in the cocaine group compared to the alcohol groups (Go-nogo [Task 3]); (ii) the alcohol group would be more sensitive to negative feedback and as a result, a decrease in performance was expected as a result of errors on a speed performance tasks (Go-nogo Error [Task 3]).

6.5 Methods

6.5.1 Sample

Participants were in-patients of a private drug/alcohol treatment clinic situated in Somerset West, South Africa. The study sample consisted of 73 abstinent patients, aged 18-

60, diagnosed with alcohol and/or cocaine dependence who were recruited for a larger study (Young et al., 2016). Patients with a primary diagnosis of alcohol and/or cocaine dependence who had been detoxified were included. Patients who met criteria for abuse (lifetime or current) of other substances were included, provided that these were not their primary drugs of use/abuse. Patients who met criteria for dependence on any substance other than cocaine/alcohol were excluded. For the alcohol group, patients were excluded if they had a current or past history of dependence on cocaine. For the cocaine group, patients with a current or past history of alcohol dependence were excluded.

6.5.2 Procedures

Participants were all inpatients (n=74) at a private treatment programme at Momentum Mental healthcare South Africa for AUD and/or CUD at a treatment clinic in Somerset West, South Africa. The clinic offers treatment to individuals mainly of Dutch nationality (main patient referral company is situated in the Netherlands). The clinic offers a comprehensive primary care treatment program which centres on an 8-week cycle and offers a group of therapies, individual counselling, written work and a psycho-educational lecture series. All participants worked with an individual therapist who guided them through the process.

The treatment program formed part of the standard of care for all participants. A full medical examination was conducted on every patient at the clinic (toxicology + biochemistry reports and physical examination by the residential psychiatric nursing staff). Participants were tested at three points in time: (i) within 72 hours of entry into the treatment programme, (ii) after completion of the treatment programme at eight weeks (measure of treatment response), and (iii) at 12-month follow-up sessions (measure of relapse). Designated counsellors at the clinic enquired from patients about their potential interest in study participation. Only participants who gave written consent and were eligible on screening were invited for a first research visit.

After written consent was obtained, the Measurements in the Addictions for Triage and Evaluation.2 (MATE.2.10) (Schippers, Broekman, Buchholz, Koeter, & Van Den Brink, 2010), a semi-structured diagnostic interview (MINI) (Lecrubier et al., 1997), and a socio-demographic questionnaire were administered. Two study visits were conducted at the clinic. Each of these visits entailed filling out self-report questionnaires and experimental motor task testing. All assessments were conducted in a structured manner by either the PI, or a trained research assistant. One research assistant was appointed for a period of 2 years. For quality control, all questionnaire and task performance scores, including data entry, were cross checked by both the PI and the research assistant. For the administration of all assessments, standard Operating Procedures (SOPs) were followed. Task instructions were read out in the same way to each participant (for the SOPs and instructions that were read out for the neuropsychological testing, see appendix A; for Motor task testing, see appendix B). The same order of assessment was used for each visit and for each participant.

To reduce temporal perception variability (Matthews & Meck, 2014) in our experimental context, all assessments were carried out in the same research space and in the same order in accordance with a standard operational procedure, with instructions read out to participants. After completion of the baseline visit, an appointment for a second assessment was made. Both assessments were undertaken within 72 hours of initiation of the treatment program and repeated at the end of the eight week (last 72 hours). Participants were followed up at 12 months as part of the larger study. Here, we report on the baseline assessments only.

6.5.3 Measures

This included the collection of data on gender, age, handedness, ethnicity, education, family history of substance dependence, previous admissions/counselling/therapy history, drug or alcohol usage (period of abstinence, physical complaints and craving), level of depression, self-efficacy to abstain from substance use, comorbid disorders (including comorbid symptoms severity), impulsivity, quality of life, estimated level of intelligence, intake and discharge report, the Edinburgh Handedness Questionnaire (EHQ) (Büsch et al., 2010),

the *Nederlandse Leestest voor Volwassenen* (NLV) (Schmand et al., 1992), the MATE.2.10 Outcomes Measurement (Schippers et al., 2010), Mini International Neuropsychiatric Interview version 5 (MINI 5) (Lecrubier et al., 1997), the Alcohol Use Disorders Identification Test (AUDIT) (Lundin et al., 2015) and the Drug Use Disorders Identification Test (DUDIT) and (Hildebrand, 2015).

6.5.4 Motor timing: Action-based timing tasks

The motor tasks consisted of a series of reaction-prediction visuo-motor pointing tasks to measure different aspects of motor timing (motor sequencing, synchronisation, and inhibition). The sequential pointing tasks were all designed by Professor Y. Delevoye-Turrell and her team at the University of Lille, France. These tasks have been used in previous research but not in SUD research (Delevoye-Turrell et al., 2007, 2012, Dione et al., 2013, 2005; Dione & Delevoye-Turrell, 2015). For testing, participants were seated in front of a tactile screen (Elo Touch) of 53cm by 36cm by 30 cm which was placed close to the participants' midline in order to avoid muscle fatigue from the repetitive pointing movements. Visual and auditory signals were controlled via a PC with coded software in C++. For a detailed overview of these tasks, please see the protocol publication (Young et al., 2016)

6.5.4.1 Reactivity: the motor reaction task

When it comes to accurately execute spaced and timed reactions, subjective representation of time is crucial (Avanzino et al., 2013; Bortoletto et al., 2011; Bortoletto & Cunnington, 2010). In order to act successfully, millisecond (m/sec) range timing task sequences need to be planned before the movement is executed (Bortoletto et al., 2011). Naturally, increased sequence complexity, carried out under time constraints, should result in faster movement times. In sum, rhythm and movement initiation are processed into an action plan before the movement occurs (Bortoletto & Cunnington, 2010). Measuring reaction and movement time abilities, whilst carrying out millisecond movement sequences, in increasing complexities, allows for the measurement of motor planning abilities. The task used for this

purpose, the Motor Reaction Task, evaluated this ability using a simple finger-pointing task to visual dots presented on the touch screen. Participants are required to lift (action initiation- measured as Reaction Time) and touch (action execution- measured as Movement Time) one dot (condition one), a series of two (condition 2) or of 3 dots (condition 3).

Manipulation of the complexity (the number of dots) of the motor sequence provides the means to assess lower order timing mechanisms (one target) and higher order mechanisms (2 and 3 dots) through the capacity of participants to structure, organize and plan an action through time and space by ensuring accurate pointing in combination with fast movements. Condition one is designed to measure lower order mechanisms of movement initiation and execution, whereas conditions 2 and 3 are designed to measure higher order mechanisms through increased complexity which requires structuring and planning of motor timing. Participants are instructed to start with the index finger of the dominant hand placed on the square starting zone which is situated at the bottom left edge of the screen. As soon as a black dot appears on the screen, the task is to lift off from the central target (square) and touch the target(s) as fast as possible. Three levels of complexity were counterbalanced: one target; two-target or three-target conditions. With regards to general motor timing abilities, we expected to find decreased in motor movements with increasing sequence complexity (number of targets) for all participants.

6.5.4.2 Decision-making: the Go-nogo task

In order to achieve positive outcomes in the future and function effectively, the urge for immediate gratification has to be postponed and goal directed behaviour given preference (Zimbardo & Boyd, 1999). To do this effectively and efficiently, cognitive control is necessary. Flexible goal-directed behaviour requires an adaptive cognitive control system for selecting contextually relevant information and for organizing and optimizing information processing. A modified version of the Go-nogo paradigm was designed to measure reaction times through

a tactile touch of the touch screen. The starting zone is situated at the bottom left edge of the screen. The target is a white circle with a black letter or one-digit black number, and participants are instructed to act as fast as possible (Go) or refrain from acting (Nogo), depending on the condition of the task. In the first condition, the task is to tap the target that appears as fast as possible (100% Go). In the following blocks, participants are instructed to also react and tap the target as fast as possible, but only if the target is a letter (50 % Go). If the target is a number, they are to refrain from reacting. Numbers and letters were presented in semi-random order. The targets are presented for 5s on the screen, with a random phase lag of ± 300 ms in order to avoid anticipatory responses. To assess cognitive control types, the reaction times obtained after a Go Target (of both Go (1) and Nogo (2) conditions), after a Nogo Target, and after a Nogo Target error (i.e. touched the Nogo Target) were used. Cognitive control was measured through decision making (reaction time after Go Targets and Nogo Target) and adaptability (reaction time after a Nogo Target Error). We expected cognitive control to be expressed as a measurable attempt to avoid making error, or adapting after an error has been made through faster reaction times after a Go Target compared to reaction times after a Nogo Target and a Nogo Target Error indicating control over behaviour.

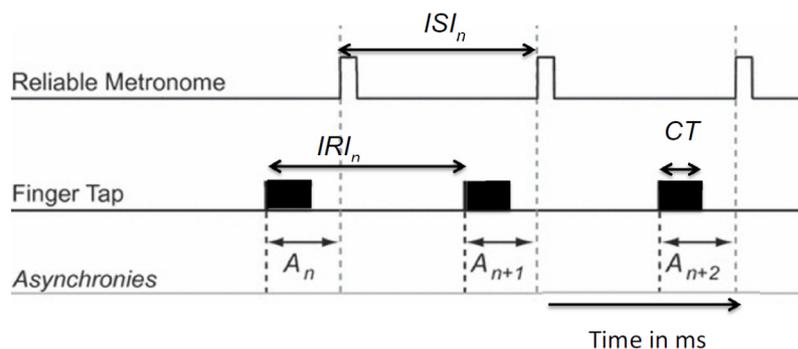
6.5.4.3 Synchronisation: the Spatial-tapping task

Sensory motor synchronization is defined as the ability to synchronise motor output with sensory input (Iversen & Balasubramaniam, 2016). Synchronisation tasks entail finger-tapping and circle drawing paradigms (Yvonne, Repp, Dione; Repp, 2013) and measure the coordination of Synchronising rhythmic movements to an external rhythm (for a review see Repp, 2013). The Spatial-tapping task (Dione et al., 2013), a hybrid finger tapping-circle drawing task, evaluates how well self-initiated actions to external stimuli are timed (synchronised) in both time and space. We measured pointing accuracy in time and space as well as error in fluency and accuracy. Six black dots were presented on a tactile screen display

100 mm apart in a circle. The instruction was to touch each target, one after the other, starting from the bottom right target, and moving counter-clockwise using the right index finger (fist closed).

Each condition is constituted of a series of sixty taps of, in total, 5 trials. The total duration of the task is approximately 10 minutes. There are two experimental conditions: one using the participants own 'spontaneous' rhythm, and the other where different tempi (ISI= 1100m/sec; 700m/sec, 500m/sec, and 300m/sec) are fixed in terms of inter stimulus intervals (ISI). The ISI is considered an important independent variable in timing research (Repp & Su, 2013). In condition two, the auditory rhythm was used to pace their actions. After listening to the tones for 5.5s, participants started tapping for a total trial duration of 35s. Timing performances on this task were measured through Inter-response interval errors (IRI error) and Synchronisation errors (Asynchrony) were measured through the difference between onset of a tap and the time of onset in the external rhythm. The IRI was measured as the time intervals between the start of two successive taps and computed as the percentage of absolute difference between each IRI and the reference inter-onset interval (ISI) of a given trial. See Figure 6.1 for a visualisation of the two timing variables (IRI errors and Synchronisation errors). Spatial performances were measured through the measurement of endpoint distributions of pointing actions and were plotted as a function of each visual target position. The mean spatial error (SE) of these spatial ellipses was used as an indication of spatial performances (Dione & Delevoeye-Turrell, 2015). The control of pauses was measured through contact time (CT) and defined as the time of finger contact with the touch screen. This measure (in m/sec) was used as an indicator of the amount of voluntary pauses in the gesture. Normal range of motor timing would be expressed as poorer ability to accurately time movements at higher tempi (IRI Error), poorer ability to keep a rhythm at fast tempi (Asynchrony), more spatial errors (SE) at faster tempi and higher contact times (CT) at slower tempi.

Figure 6-1 Visual overview of Inter response interval, Inter Stimulus interval, Asynchrony and Contact



Note: IRI - Inter response interval, ISI - Inter Stimulus interval, A - Asynchrony, CT, Contact Time

6.6 Data Analyses

Two types of analyses were conducted. First, analyses comparing patients with HC were undertaken. Second, patient groups were compared, excluding HC. Potential confounding group variables were compared using *Analyses of Variance* (ANOVA). Age was found to significantly differ between groups and was controlled for in subsequent analyses. In the Motor Reaction Task, 2-way ANOVA was conducted with Condition and Group as factors. Motor sequencing was examined on three levels of complexity: 1 Target; 2 Target or 3 Target Conditions. In all Conditions, we calculated the means and standard deviations for Reaction Time (time between target presentation and finger lift off of the square) and Movement Time (time between finger lift off of the square, after target presentation, and touch of the first target). In the Go- nogo task, two-way *Analysis of Covariance* (ANCOVA) was conducted, assessing Target and Group and using Age as a covariate. Target was used to indicate a type of cognitive control: control of reacting to Go trails to Nogo trails, and the control to adapt after Nogo errors were made. Target was calculated using reaction times on trails after different Go-nogo stimuli

types were presented. As such, Target was calculated as follows: (i) reaction time after a Go Target (react), after a Nogo Target (refrain), and after a Nogo Target Error (adapt). In the Spatial-tapping task for condition 1, the data was not normally distributed, and an independent samples Mann Whitney U test was conducted.

For the patient group analyses in condition 1, an ANOVA was conducted. In condition 2, 3-way ANOVA were conducted using ISI, Group and Synchronisation abilities (IRI Error, Asynchrony, CT, and SE) as factors in both analyses. Synchronisation abilities were measured on two levels (time and space). With regard to time, IRI errors were computed as the percentage of absolute difference between each IRI and the ISI of a given trial. Synchronisation errors (Asynchrony) were calculated from the difference between onset of a tap and the time of onset in the external rhythm. With regard to spatial abilities, the endpoint distributions of the pointing actions were plotted as a function of each visual target position. Through vector calculations, spatial ellipses were then calculated. The mean SE of the spatial ellipses was measured in mm² (Dione & Delevoye-Turrell, 2015). CT was measured in milliseconds.

6.7 Results

Please see Table 6.1 for sample characteristics. See Table 6.2 for an overview of motor task results.

Table 6-1. Sample characteristic means and standard deviations of the complete sample, individual groups, and group comparisons where appropriate.

	N=74		Alcohol		Cocaine		Alcohol/Cocaine		All patients		Control group	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age	44.2	.8	32.8	.9	32.8	.9	37.1	11.1	36.4	13.7		
Alcohol Use last 30 days	18.5	10.1	4	5.3	16.6	8.3	13.1	10.3	-	-		
Alcohol quantity used last 30 days (units)	15.2	9.6	5.7	7.4	16.4	15.6	12.6	12.3	-	-		
Cocaine Use last 30 days	10.8	.2	15.3	10.6	10.8	9.7	8.8	10.4	-	-		
Cocaine quantity used last 30 days (grams)	.04	.1	3.2	3.4	1.3	1.4	1.5	2.5	-	-		
AUDIT	25.3	8.9	8.2	5	24.6	7.5	19.6	10.7	3.9	3.4		
DUDIT	7	8.1	31.5	7.6	28.6	8.8	23.6	13.2	.40	1.1		
Sheehan	16	7.1	21.4	6.3	17.4	9	18.6	7.8	-	-		
BIS*	84.1	11.6	93.6	12.6	98.4	13.9	92.4	13.9	64.6	5.1		
Duration of Use*	24.2	11.9	12.4	7.6	15.2	8.3	17.3	10.3	-	-		
Age of first Use	20.5	9.3	20.9	5.5	17.3	4.1	19.6	6.8	-	-		
Abstinence in days	16	14.1	14.6	12.1	14.2	10.43	14.9	12.2	-	-		
GAF score at admission	52.8	6.9	51.5	11.7	52.5	7.5	52.3	8.9	-	-		
Physical Complaints	12.2	6.8	9.1	8.4	11.6	7.7	11	7.6	-	-		
Craving (last 30 days)	6.7	3.3	7.9	4.2	7.8	4.2	7.5	3.9	-	-		
Comorbid Symptom Severity	19.1	12.9	21	11.7	22.3	13.5	20.9	12.6	-	-		

Note: Results of separate groups; IQ: Nederlandse Leestest voor Volwassenen indication of intelligence, AUDIT: Alcohol Use Disorder Identification Test, DUDIT: Drug Use Disorder Identification Test; Quality of Life, Sheehan Disability Scale (SDS), Impulsivity, (BIS) Behavioural Inhibition Scale; GAF: Global Assessment of Functioning. MATE 5; Measurements in the Addictions for Triage and Evaluation, Physical Complaints/health related symptoms in the last 30 days; MATE Q1, Measurements in the Addictions for Triage and Evaluation, Craving Scale regarding the last 30 days; MATE Q2, Measurements in the Addictions for Triage and Evaluation, Anxiety, Depression, Stress Scale last 30 days.

*Post hoc analyses revealed that the Alcohol group was significantly less impulsive compared to both the Cocaine and Alcohol/Cocaine groups, the Cocaine and Alcohol/Cocaine groups did not differ significantly. The controls were not included in this comparison.

** The Alcohol group had a significantly higher duration of use compared to the Cocaine and Alcohol/Cocaine groups. The Cocaine and Alcohol/Cocaine groups did not differ significantly. Since age if first use did not differ significantly we did not control for this in further analyse.

Table 6-2 Means and standard deviations of all motor tasks performances of the patient group comparisons and the patient control group comparisons

			Patient group comparisons						Patient and control group comparison			
			Alcohol		Cocaine		Alcohol/Cocaine		All patients		Controls	
			<i>n</i> =25		<i>n</i> =24		<i>n</i> =24		<i>n</i> =25		<i>n</i> =24	
			<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Go-nogo task	Reaction Time	After Go	.66	.51	.42	.04	.51	.18	.51	.01	.54	.02
		After Nogo	1.28	1.74	.65	.41	.68	.45	.59	.11	.85	.07
		After Nogo error	.47	.72	.24	.27	.35	.34	.28	.03	.55	.07
Finger Tapping Task	Space	Spontaneous ISI	494.85	140.58	401.05	99.26	451.53	120.90	451.53	120.90	432.89	81.79
		Contact Time (m/sec)	.15	.07	.11	.02	.15	.04	.14	.01	.15	.01
	Interval timing Time	Spatial Error (%)	11.3	3.3	13.7	3.7	11.7	2.7	12.2	.41	15.1	.58
		Asynchrony (%)	-.05	.08	-.03	.06	-.04	.07	-.04	.01	-.02	.01
	Space	IRI error (%)	6.7	2.3	7.1	3.2	6.8	2.8	7.1	.18	6.5	.26
		Contact Time (m/sec)	.20	.13	.16	.10	.19	.12	.18	.01	.16	.01
		Spatial Error (%)	11.4	3.5	11.6	3.2	11.1	3.2	11.6	.22	14.1	.34
Motor reaction task	Movement Initiation	1 target (m/sec)	.40	.07	.41	.08	.40	.06	.40	.01	.40	.01
		2 targets (m/sec)	.41	.06	.41	.07	.41	.06	.41	.01	.40	.01
		3 targets (m/sec)	.40	.05	.41	.07	.40	.03	.40	.01	.40	.01
		All targets (m/sec)	.40	.06	.41	.06	.40	.07	.40	.01	.40	.01
	Execution	1 target(m/sec)	.36	.09	.38	.09	.43	.13	.39	.01	.40	.01
		2 targets(m/sec)	.34	.07	.33	.08	.35	.07	.33	.01	.34	.01
		3 targets(m/sec)	.34	.07	.31	.07	.33	.07	.32	.01	.33	.01
		All targets (m/sec)	.35	.08	.36	.10	.33	.08	.35	.01	.36	.01

6.7.1 (i) Patient versus Healthy Controls

For this analysis, all patients were combined and compared with HC.

6.7.1.1 Reactivity (Motor Reaction Task)

With regard to Reaction Time (movement initiation), no effects were found between patient and Hc groups. With regard to Movement Time (movement execution), a main effect was found for Condition ($F(2,203) = 56.7, p < .01$). Post hoc analyses revealed that participants moved significantly slower in Condition 1 (a single target) compared to 2 (two targets, *Mean difference* = .06, *Std error* = .01, *CI* = .04-.07, $p < .01$), and Condition 1 and Condition 3 (three target, *Mean difference* = .06, *Std error* = .01, *CI* = .05-.08, $p < .01$), but not between Conditions 2 and 3. No main effect for Group and no interaction effects were found for Group and Condition on Movement Time.

6.7.1.2 Decision making- the Go-nogo task

A main effect was found between groups on reaction time obtained after a Go Target ($F(1,102) = 15.49, p < .01$). Patients had significantly faster reaction times ($M = .53, SD = .03$) compared to HC ($M = .54, SD = .01$). A significant effect was found on reaction time after a Nogo Target Error ($F(1,85) = 7.49, p < .01$), with the patient group exhibiting faster reaction times after an error was made ($M = .32, SD = .32$) compared to controls ($M = .54, SD = .06$). No Group effect was found on reaction time after a Nogo Target.

6.7.1.3 Synchronisation: The Spatial-tapping task

Timing performances in time and space were examined through different interval timing task conditions. In the spontaneous rhythm condition, only spatial abilities (CT and SE) were assessed.

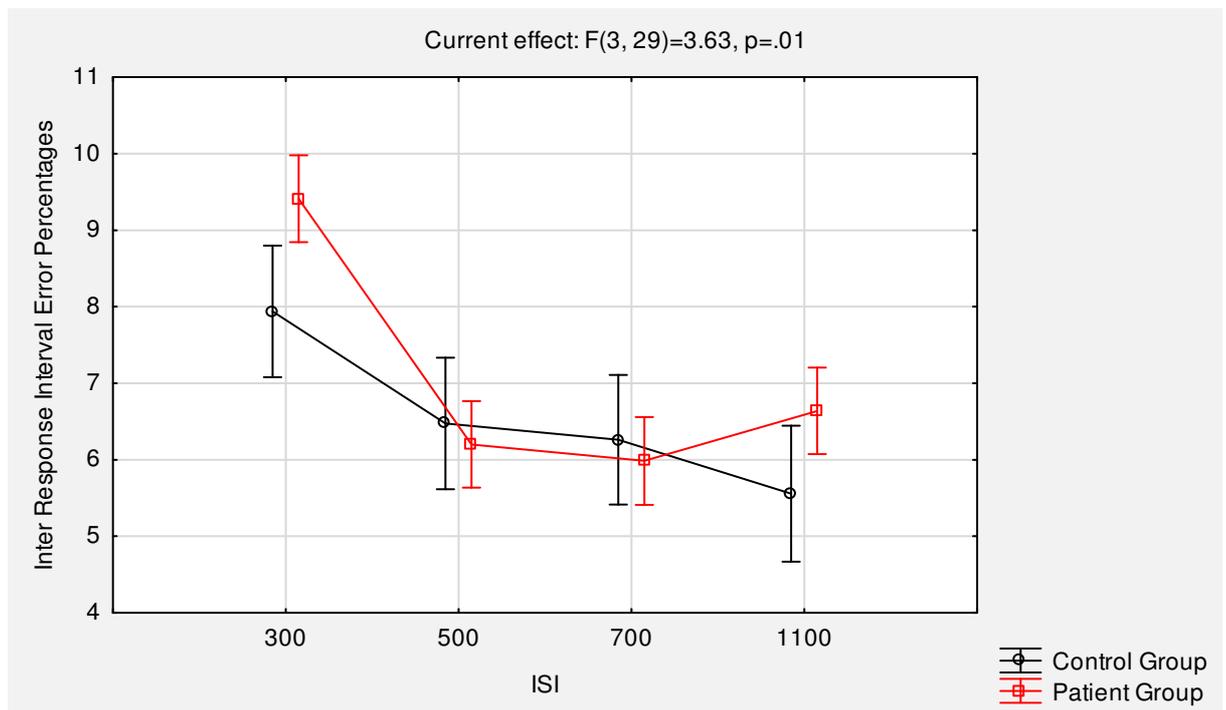
6.7.1.3.1 Spontaneous rhythm- Contact Time and Spatial Error

An independent sample T-test *Mann-Whitney U Test* showed no significant differences between the spontaneous ISI of the patients and the HC. No main effect was found for Group on CT using the participant's spontaneous rhythm. With regard to SE, a main effect was found for Group $F(1,92) = 15.787, p > .01$. SE in the patient group ($M = 12.2, SD = .41, CI = 11.4; 13.08$) were lower than the control group ($M = 15.1, SD = .58, CI = 13.9; 16.24$).

6.7.1.3.2 Timing abilities during interval timing- IRI Error and Asynchrony

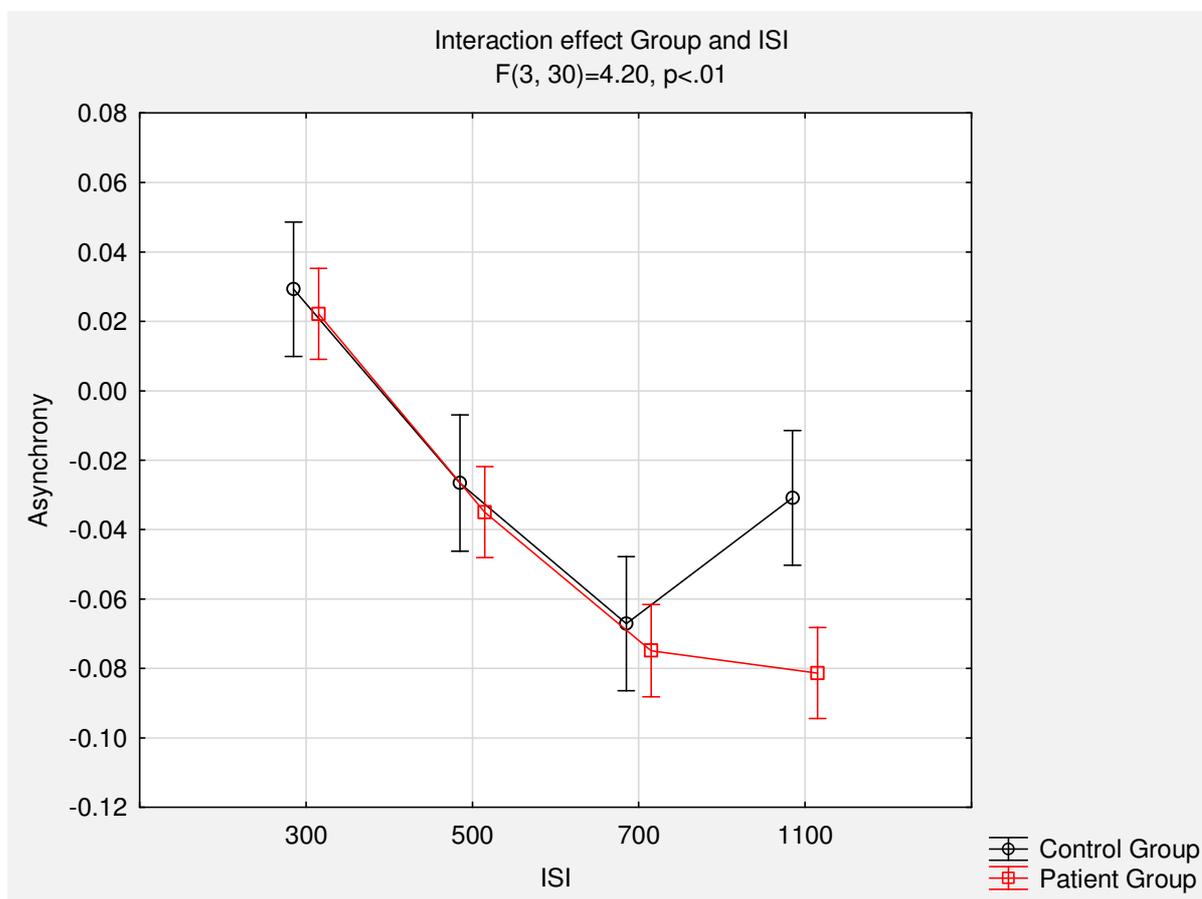
A significant ISI effect on IRI error percentages was found ($F(3,29) = 27.44, p < .01$). Participants had higher IRI Error percentages at ISI 300 compared to ISI 500, 700 and 1100. No main group effect was found in IRI errors. An interaction effect was found for group and ISI ($F(3, 29) = 3.6, p < .01$, see figure 6.2) on IRI errors was found. Controls made significantly fewer errors than patients on ISI 300 (*Mean Difference* = -1.47, *Std error* = .52, *CI* = -2.50; -.44, $p < .01$) and ISI 1100 trails (*mean difference* = -1.08, *Std error* = .53, *CI* = -2.13-.02, $p = .04$, see figure 6.2).

Figure 6-2. Group and ISI interaction effect of the Patient and Healthy Control comparison



A main effect was found for group on Asynchrony ($F(1, 104) = 5.67, p < .03$). The patient group made more error ($M = -.04$, Std error = .01, CI = -.05; -.03) than the HC ($M = -.02$, Std error = .01, CI = -.03; -.01). A main effect for ISI was found ($F(3, 30) = 6.63, p < .01$). All ISI combinations were significantly different in error percentages ($p < .01$). An interaction effect for group and ISI ($F(3, 30) = 4.18, p < .01$) was found. ISI 1100 controls performed better than patients ($mean\ difference = .05$, Std error = .01, CI = .02-.07, $p < .01$). See figure 6.3.

Figure 6-3 Interaction effect between Group, Tempi and Asynchrony



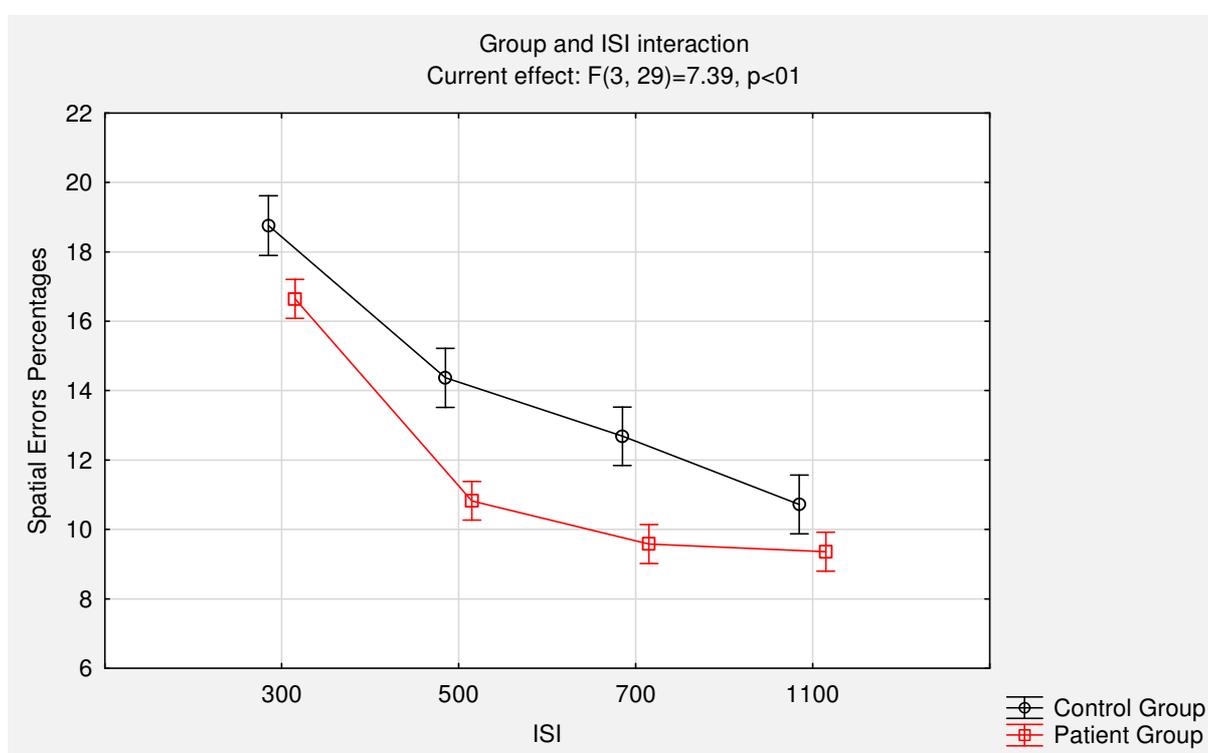
6.7.1.3.3 Spatial abilities on interval timing- Contact Time and Spatial Error

For CT, a significant ISI effect ($F(3,30) = 56.59, p < .01$) was found. All combinations (ISI 300, 500, 700, 1100) were significantly different from each other ($p < .01$). No group or interaction effects were found for CT.

With regard to SE, a main effect was found for Group ($F(1,10) = 37.84, p < .01$, see figure 6.3). The HC group had higher SEs ($M = 14.13, Std\ error = .034$) compared to the patient group ($M = 11.60, Std\ error = .22$). A main effect was found for ISI ($F(3,29) = 344.03, p < .01$). SE were larger at faster ISI. All ISI combination comparisons

were significant ($p < .01$). An interaction effect for group and ISI ($F(3, 29) = 7.39$, $p < .01$) was found. Patient groups made less SE on ISI 300 (*mean difference* = 2.11, *Std error* = .52, *CI* = 1.08; 3.13, $p < .01$), ISI 500 (*mean difference* = 3.54, *Std error* = .51, *CI* = 2.52; 4.56, $p < .01$), ISI 700 (*mean difference* = 3.10, *Std error* = .51, *CI* = 2.09; 4.11, $p < .01$) and ISI 1100 (*mean difference* = 1.36, *Std error* = .51, *CI* = .35; 2.37, $p < .01$). See Figure 6.4 for an overview of these results.

Figure 6-4 Spatial error differences between the healthy control and the patient groups



6.7.2 (ii) Patient group comparisons

For these analyses, HC were excluded. Patient groups were compared with each other. Please see Table 6.2 for the means and standard deviations of performances on all tasks pre- and post-treatment.

6.7.2.1 Reactivity: the Motor Reaction Task

With regard to Reaction Time (movement initiations), no main effect for Group or Condition were found. With regard to Movement Time (movement execution), no main effect for Group or Condition were found. No interaction effect was found for Group and Condition on either Movement Time or Reaction Time.

6.7.2.2 Decision making- the Go-nogo task

A main effect was found between groups on reaction time obtained after a Go Target ($F(2.69) = 7.01, p < .01$). Post Hoc analyses revealed significant differences between the CUD and AUD groups ($p < .01$) and the CUD and AUD/CUD groups ($p < .01$). The CUD group had the fastest reaction times of all groups. No Group effect was found on reaction time after a Nogo Target. No significant Group effect was found on reaction time after a Nogo Target Error.

6.7.2.3 Synchronisation: The Spatial-tapping task

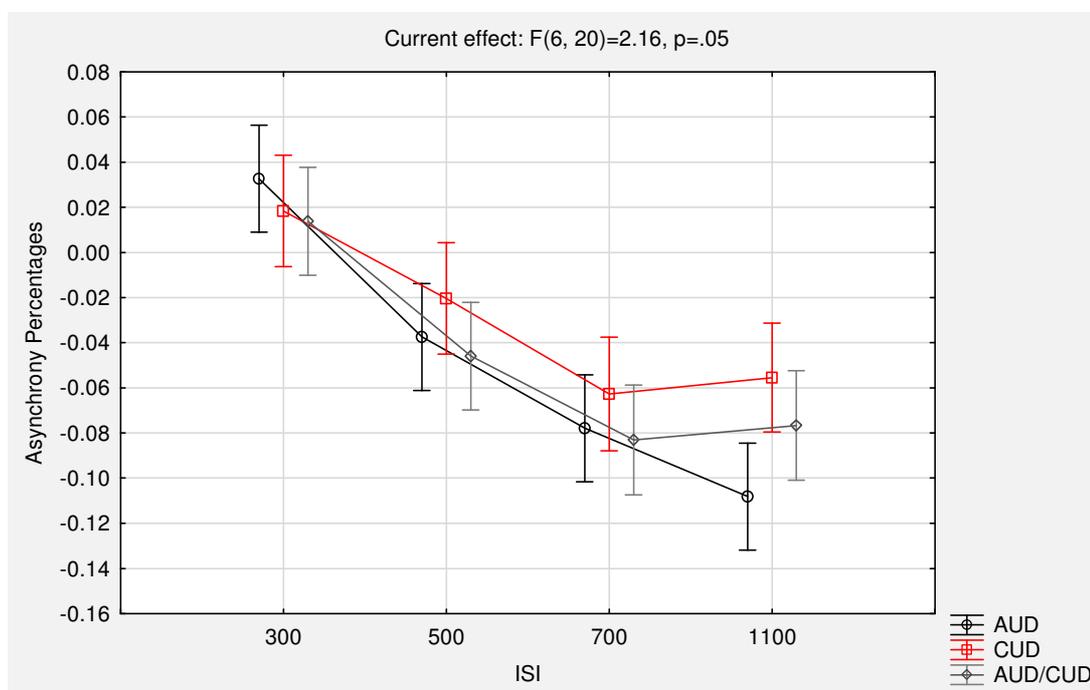
6.7.2.3.1 Spontaneous rhythm- Contact Time and Spatial Error

An Analyses of Variance (ANOVA) was conducted to compare Group on Spontaneous ISI. There was a significant effect for Group ($F=2.461) = 3.36, p=.04$). Post hoc analyses showed that the AUD ($M=494.85, SD=140.58$) and CUD ($M= 401.05, SD=99.26$) groups differed significantly ($p=.01$). The other group comparison results were not significant. With regard to spatial abilities, a main effect for Group on CT using spontaneous rhythms was found $F(2, 59) = 4.8823, p=.02$. Significant differences were found between the AUD and CUD groups ($p < .01$) and the AUD/CUD and CUD groups ($p < .01$). With regard to SE, no main effect was found for Group.

6.7.2.3.2 Timing abilities during interval timing- IRI Error and Asynchrony

A significant ISI effect in IRI error percentages was found ($F(3,203) = 30.74, p < .01$). Participants had higher IRI Error percentages at ISI 300 compared to 500, 700 and 1100 ISI. No group effect was found, and no interaction effect was found for group and ISI. Main effect found for ISI ($F(3,203) = 63.03, p < .01$) for Synchronisation. Synchronisation errors on ISI 300, 500 and 700 differed significantly from each other ($p < .01$). Error percentages on ISI 700 and 1100 did not significantly differ from each other. An interaction effect for Group and ISI was found ($F(6,203) = 2.16, p = .04$). Post hoc analyses revealed that error percentages in ISI 1100 differed significantly between the CUD and AUD groups ($\text{mean difference} = -.05, \text{SD error} = .01, \text{CI} = [-.08; -.01], p < .01$). See figure 6.5 for an overview of the Asynchrony Group and ISI interaction.

Figure 6-5. Patient group comparisons, ISI interaction effect on synchronization error percentages



Note. AUD, Alcohol Use Disorder; CUD, Cocaine Use Disorder; AUD/CUD, Alcohol and Cocaine Use Disorder. The AUD and CUD groups differed significantly at ISI 1100. The CUD group performed better compared to the AUD group

6.7.2.3.3 Spatial abilities on interval timing- Contact Time and Spatial Error

For CT, a significant ISI effect ($F(3,302) = 56.59, p < .01$) was found. All combinations (ISI 300, 500, 700, 1100) were significantly different ($p < .01$). No group or interaction effect was found.

With regard to SE, a main effect was found for ISI ($F(3,203) = 331.10, p < .01$). SE were larger at faster ISI. SE on ISI 300, 500 and 700 differed significantly from each other ($p < .01$). SE on ISI 700 and 1100 did not significantly differ from each other. No main or interaction effect was found for Group and group and ISI.

6.8 Discussion

We sought to explore and compare deficits in motor timing in AUD and/or CUD populations compared with a matched HC group. The use of this motor task battery resulted in findings in support of deficits in the GM and less so in the DM. With regard to the DM, no indication of a faster internal rhythm was found amongst patients compared to HC. The capacity to structure, organise and plan an action directly towards a visual target was also unaffected. We did find support for van Hoof's model through higher reaction times after a Go Target on the Go-nogo task and higher reaction times after Nogo Errors were made in the patient groups. With regards to the GM we found a lower capacity to make internal representations in individuals with SUD compared to HC. As mentioned, no deficits in control were found when actions were inhibited successfully; however, this control seemed to diminish once errors were made. This is in line with van Hoof who suggests that a weakened GM could lead to imbalance in behaviour. A possible explanation could be that errors are perceived as stressful and lead to increased cognitive load and, subsequently, a loss of control over inhibition. In fact, all deficits found seem to only occur when cognitive load was increased. Patients were less able to accurately and fluently synchronise at tempo extremities (fastest and slowest). With regard to

individual differences between patients, we found that the CUD group had a comparatively lower inhibitory capacity compared to the AUD group. We did not, however, find an increased sensitivity to negative feedback or the expected decrease in performance on Go-nogo Error Targets.

With regards to general (normal) motor timing abilities in the sample as a whole, all expectations of the task battery were met. We found decreased motor movements with increasing sequence complexity (number of Targets [Spatial-tapping task]): poorer ability to accurately time movements at higher tempi (IRI Error), poorer ability to keep a rhythm at fast tempi (Asynchrony), more spatial errors (SE) at faster tempi and higher contact times (CT) at slower tempi. We also found that cognitive control was expressed as a measurable attempt to avoid making errors or adapting after an error had been made - expressed as faster reaction times after a Go Target compared to reaction times after a Nogo Target and a Nogo Target Error and indicating control over behaviour. In sum, planning and motor coordination differences were not observed between patient groups and patients and HC.

With regard to decision-making, significantly higher reaction times were observed in the patient groups compared to HC, thus supporting van Hoof's model that individuals with an SUD may in fact have an overactive DM. No differences in reaction times were found after Nogo Targets between HC and patients nor between patient groups. This indicates that whilst reaction times are generally higher in patients, especially individuals with CUD, their ability to inhibit is similar to non-pathological groups. Interestingly once an error is made, reaction times speed up significantly in patients versus HC. In sum, no deficits in cognitive control was found when actions had to be inhibited; however, this control seemed to diminish once errors were made. A possible explanation could be that errors are perceived as stressful and lead to increased cognitive load and, subsequently, a loss of control over inhibition.

When participants were asked to execute the Spatial-tapping task, in absence of an external rhythm, we noted the following: Firstly, contrary to what we expected, spontaneous rhythms did not differ between patients and HC. This was unexpected also in light of the

average reaction times on the Go-nogo task, which did differ, with patients reacting much faster. A possible explanation could be the lack of cognitive demands on this part of the task. Participants were asked to move at a pace most convenient/comfortable to them, whereas the Go Target of the Go-nogo task demanded attention to possible Nogo Targets, accompanied by the instruction to react as soon as the targets were presented on the screen. Again, this cognitive demand could be reason for the differences observed. The spontaneous rhythm condition did yield differences between patient groups. The Cocaine group had the fastest overall spontaneous tempo, possibly indicating a faster internal clock compared to AUD and AUD/CUD groups. The spontaneous rhythm condition resulted in differences with regard to spatial abilities between the groups. An unexpected finding was that patients made fewer spatial errors compared to HC whilst the contact durations remained similar (CT). The patient groups did not differ on spatial error rates whilst the durations of touch (CT) was found shorter in the CUD group compared to the other patient groups. This difference can be explained by overall faster spontaneous tempo of movement in this group (CUD) which would result in expected shorter contact durations, as would be expected based on normal movement.

When participants were asked to synchronise movements to a tone in the following condition, the following were noted: Firstly, all participants performed with increasing inter response error rates at faster tempi- which is a normal human movement capacity- and no group differences were found in this regard. However, patients performed poorer at the highest (300m/sec) and lowest (1100) tempi. In patients, this may be due to the increased cognitive load at very fast tempi (fast motor movements combined with accuracy) and slow tempi (accuracy in timing with regard to memory). With regard to the ability to synchronise, the ability to synchronise to a tone corresponded with the average spontaneous rhythm of all participants (442 ISI). All participants touched targets slightly before objective time (the tone) at faster tempi (300 ISI) and ahead of objective time beyond that (ISI >500). This is expected normal motor timing behaviour. Patient-HC group comparisons, however, showed that the patient group performed worse than the HC. Individual tempi and patient group comparisons

showed that controls performed better than patients at 1100 ISI. Further group comparisons showed that error percentages in ISI 1100 differed significantly between the CUD and AUD groups but not the CUD and AUD/CUD or AUD and AUD/CUD groups. The difference between patients may be due to increased cognitive load due to the having to make predictions about accurate timing of movements.

With regard to spatial abilities, we found that CT was not significantly different in HC and patient groups, nor among patient groups, in conditions in which movement had to be synchronised to external input. This supports the assumption we made to explain the increased CTs in the Cocaine group when spontaneous rhythms were used (i.e., that CT shorten at higher tempi). SEs did differ (on all tempi) between patient and HC group, with patients performing better than the HC. The patient groups did not differ on SEs. Interestingly, the repeating pattern (in self-paced and synchronised movements) of patients outperforming HC on spatial accuracy but not each other on this task, was intriguing. Considering that patients overall performed more poorly on all other timing abilities, this finding may have significant implications for future studies. Since the spatial accuracy component of this task heavily relies on visual feedback during performances (visual feedback is used to enable successful task execution by touching the dots in a circular motion), spatial errors observed in movement may indicate compulsivity in motor timing. As there are many temporal processing assessment tools available to date and few to assess compulsive behaviour, we encourage future researchers to further explore these findings.

6.9 References

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7 Neurocognitive Performance as a Predictor of Motor Timing in SUD Populations

Chapter 7 presents the findings from the secondary aims of this study. The study aimed to assess the patient data as a whole. Motor timing performances were correlated with impulsivity. Regression analyses were used to assess the effects of working memory and attention on motor timing. The chapter has been presented here in the format of a manuscript, as this section will be submitted for publication.

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7.1 Abstract

Introduction: Over the past years, there has been a growing interest in neuropsychological deficits in patients with Substance Use Disorders (SUD). Besides deficits in working memory (WM), impulsivity and attention, individuals who chronically use substances of abuse that have neurotoxic effects on frontostriatal areas in the brain, experience motor timing deficits. It is unclear whether observed temporal processing deficits, in fact, reflect increased sustained attention or WM demands (which are required by timing tasks) or whether motor timing deficits reflect a separate entity. The main questions of this study were: (i) Is motor timing explained by attention and WM? (ii) Is impulsivity related to motor timing performance in an inpatient SUD population? **Methods:** The study sample consisted of 74 abstinent patients who completed neuropsychological and motor timing test batteries. **Results:** No significant correlations were found between any of the motor tasks and impulsivity. With regard to motor timing, visual and auditory WM were significant predictors of motor timing but only for conditions that required increased cognitive demands. Attention contributed to a small portion of the variance in motor timing performance but only for spatial abilities and only at increased cognitive demands. **Conclusion:** We did not find any correlations between Impulsivity and any of our motor timing parameters. This could indicate that millisecond motor timing performances are not related impulsivity per se. Attention and WM had predictive value but only at increased cognitive demands (speed and complexity). The findings suggest that, in line with literature, millisecond timing might engage other cognitive functions on a minimal level and should be regarded as a separate neurocognitive entity. More research is needed to further investigate these preliminary findings.

7.2 Background

There has been a growing interest in neuropsychological deficits in patients with Substance Use Disorders (SUD). Findings, to date, indicate that patients with SUD are primarily guided by direct reward, are impulsive, have planning difficulties and find it difficult to foresee the consequences of their actions (Goldstein et al., 2009; Stevens et al., 2014). Cognitive deficits in SUD have been shown to influence the ability to remain abstinent and have prognostic value in SUD treatment outcomes and risk of relapse (Bates, Bowden, et al., 2013; Bates, Buckman, et al., 2013; Goldstein & Volkow, 2011; Moselhy et al., 2001; Stevens et al., 2014), which can occur after weeks, months and even years (Welberg, 2011). Craving for substances is associated with reduced frontal lobe metabolism and long-lasting changes in brain regions involved with reward processing. This could explain the loss of control over limbic impulses and denial found in individuals with SUD (Dackis & O'Brien, 2001).

Aspects of self-control, delay of self-gratification, drive inhibition, and the anticipation of consequences all require the functional integrity of the prefrontal cortex and associated executive functions (EF) (Lyvers, 2000). The pre-frontal Cortex (PFC) has a major influence on drug-taking behaviour due to its regulation of dopamine (DA) circuits and its role in executive functioning (EF) (Welberg, 2011). EF is a multidimensional construct consisting of future orientated ability to generate plans and goals, to motivate and focus oneself to execute these plans and goals and to alter these goals and plans in response to environmental changes (Suchy, 2009). Attention and working memory (WM), specifically, are domains of EF thought to impair the ability to plan ahead and consider all information available before choices are made without considering all alternatives (Arce & Santisteban, 2006). Attention and working memory (WM) deficits and Impulsivity, especially during short-term abstinence, may be particularly detrimental for patients in rehabilitation programmes due to the highly educational nature of these interventions (Bates, Buckman, et al., 2013; Gillen et al., 1998; Stevens et al., 2014) and in view of the psychosocial adaptation required of individuals in recovery (Bates et al., 2002). Furthermore, the toxic effects of alcohol and cocaine, which are

most frequently linked to neurocognitive deficits in dependent individuals (Bates et al., 2002; Moselhy et al., 2001; Potvin et al., 2014), contribute to increased disinhibition and regulation of impulsive action tendencies. Impulsivity is defined as the tendency to act rapidly and/or with diminished forethought or consideration of negative consequences to oneself and others (Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015) and is thought of as a multi-faceted construct consisting of *Rapid Response Impulsivity (RRI)* and *Choice Impulsivity (CI)*. RRI is characterized by immediate action tendencies without foresight and the lacking of context. CI is characterized by a diminished ability to tolerate delays (please refer to Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015 for detailed reviews).

There are no known psychiatric or neurological disorders primarily characterized by temporal deficits (Jennifer T Coull et al., 2011); however, timing deficits have been documented in a range of psychopathological conditions (Moreira, Wittman 2007, Fallter & Noreika, 2011) including SUDs (Morreira, 2016; Wittman, 2007). Besides deficits in working memory (WM), impulsivity and attention, individuals who chronically abuse substances that have neurotoxic effects on front-striatal areas in the brain experience motor timing deficits (Correa, Triviño, Pérez-Dueñas, Acosta, & Lupiáñez, 2010; Stevens et al., 2014; Wittmann et al., 2007). A number of human timing studies have indicated that sustained attention and working memory are crucial for accurate motor timing (Wittmann et al., 2007). Motor timing, which is defined as a component of temporal processing, regulates the generation of timed motor responses (Mauk & Buonomano, 2004). Motor timing is crucial for the proper functioning of higher order cognitive functions (Wittman, 2007), and modifications to the neural systems that support interval timing are found to contribute to cognitive dysfunction found in a number of psychopathological conditions (Meck, 2005). Indeed, the frontal lobes are believed to play a crucial role in the coding of temporal information (Grondin, 2010; Wittmann et al., 2011). Research shows that the same dorsolateral pre-frontal cells become functional for both timing and WM (Radua et al., 2014) and that EF and time perception share a common neuroanatomical basis in early development (Neufang et al., 2008).

Motor timing deficits are characterized by disruptions in PFC, hippocampus, basal ganglia and cerebellar functioning, which are brain regions that support temporal cognition and motor skill learning (Meck, 2005). Supporting this finding is research suggesting that correct EF, cognitive control and time perception are functionally and anatomically inter-related in the brain and that mechanisms of timing are modulated by attentional effort (Radua et al., 2014). One of the few studies, to date, that has attempted to examine motor timing in stimulant dependent individuals, whilst controlling for possible confounds, found that the stimulant dependent group showed abnormal motor timing abilities on all timing tasks, except sensorimotor synchronisation. However, only the over-estimation of a relatively long time interval could be explained by impulsivity, indicating that stimulant dependent individuals exhibit motor timing deficits that could not be explained by cognitive deficits (Wittmann et al., 2007). A recent review of the literature on time perception, impulsivity and decision making found that impulsive individuals perceive time differently (Arce & Santisteban, 2006; Wittmann & Paulus, 2008). Time is perceived at a higher cost, thus leading to overestimation of the duration of time intervals and consequently discounting the value of delayed rewards more strongly than low-impulsive individuals (Wittmann & Paulus, 2008). This indicates that timing deficits could also be a precipitating factor for impulsivity (Arce & Santisteban, 2006).

In sum, cognitive deficits are predictors of poor SUD treatment outcomes and relapse in alcohol and cocaine dependence, specifically (Aharonovich et al., 2006, 2003; Stevens et al., 2014; Turner et al., 2009). Attention, impulsivity, WM and timing deficits have been documented in SUDs (Goldstein & Volkow, 2011; L. Stevens et al., 2014; Antonio Verdejo-García et al., 2008; Wittmann & Paulus, 2008); however, the underlying processes that cause these deficits and their relationship is still poorly understood. Whether the observed temporal processing deficits, in fact, reflect increased sustained attention or WM demands (which are required by timing tasks), or whether motor timing is an independent process remains unknown (Jennifer T Coull et al., 2011; Ivry & Spencer, 2004). It is, therefore, important to consider timing confounds in new research paradigms (Jennifer T Coull et al., 2011). The main

questions of this study were (i) Can motor timing be explained by attention and WM? (ii) Is impulsivity related to motor timing performances, in an inpatient SUD population?

7.3 Study Aims

This study forms part of a larger study (Young et al, 2016) which aims to examine the prognostic value of motor timing deficits in SUDs. In this study, we tested if motor timing performances could be explained by different domains of executive functioning (impulsivity, WM and attention). Three contrasting motor tasks were used. The motor timing variables were correlated with impulsivity (Impulsive Choice and Rapid Response Impulsivity specifically, for a review on impulsivity see Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015) Attention and WM (visual and auditory). All patients were matched with healthy controls for age, sex and ethnicity. The tested sensitivity values of the motor timing parameters were compared to a carefully selected battery of neurocognitive tests to test the confounding effects of attention and WM on motor timing paradigms (Jennifer T Coull et al., 2011), and the high impulsivity levels found in SUDs (L. Stevens et al., 2014). This study does not only have the potential to make a valuable contribution to both the SUD and motor timing literature but could further provide knowledge of the mechanisms at play in SUDs. If motor timing has little relation to attention and WM tasks simple motor timing measures can be incorporated in the management of patients and in the monitoring of outcomes, instead of the more complicated neuropsychological testing batteries used at present.

7.4 7.2 Hypotheses

This study tested if motor timing in AUD and/or CUD populations relates to levels of impulsivity, and can be predicted by attention and WM performances. We expect to find that: i) timing deficits will correlate with measures of impulsivity (higher impulsivity reflecting higher degree of timing deficits) and ii) timing deficits will not be better predicted by attention and WM deficits.

7.5 Methods

7.5.1 Sample

Participants of this study were all inpatients at a private drug/alcohol treatment clinic situated in Somerset West, South Africa. The study sample consisted of 73 abstinent patients, aged 18-60, diagnosed with alcohol and/or cocaine dependence. Patients with a primary diagnosis of alcohol and/or cocaine dependence who were detoxified were included. Patients who met criteria for abuse (lifetime or current) of other substances were included, provided that these were not their primary drugs of use/abuse. Patients who met criteria for dependence for any substance other than cocaine/alcohol were excluded. For the alcohol group, patients were excluded if they had a current or past history of dependence on cocaine. For the cocaine group, patients with a current or past history of alcohol dependence were excluded.

7.5.2 Procedures

Participants were all inpatients at a private treatment programme for AUD and/or CUD at a treatment clinic in Somerset West, South Africa. The clinic offers treatment to individuals mainly of Dutch nationality (main patient referral company is situated in the Netherlands). The clinic offers a comprehensive primary care treatment program which centres on an 8-week cycle and offers a group of therapies, individual counselling, written work and a psycho-educational lecture series. All participants work with an individual therapist. The treatment program formed part of the standard of care for all participants, and a full medical examination was conducted on every patient at the clinic (toxicology + biochemistry reports and physical examination by the residential psychiatric nursing staff).

Participants were tested at three points in time: (i) within 72 hours of the start of the treatment programme, (ii) after completion of the treatment programme at eight weeks (measure of treatment response), and (iii) at 12-month follow-up (measure of relapse). Designated counsellors at the clinic enquired from patients about their potential interest in the study

participation. Only participants who gave written consent and who were eligible on screening were invited for a first research visit. After written consent was obtained, the Measurements in the Addictions for Triage and Evaluation.2 (MATE.2.10) (Schippers et al., 2010), a semi-structured diagnostic interview (MINI) (Lecrubier et al., 1997) and a socio-demographic questionnaire were administered. Two study visits were conducted at the clinic. Each of these visits entailed filling out self-report questionnaires and experimental motor task testing. All assessments were conducted in a structured manner by either the PI, or a trained research assistant. One research assistant was appointed for a period of 2 years. For quality control, all questionnaire and task performance scores, including data entry, were cross checked by both the PI and the research assistant. For the administration of all assessments, standard Operating Procedures (SOPs) were followed. Task instructions were read out in the same way to each participant (for the SOPs and instructions that were read out for the neuropsychological testing, see appendix A; for Motor task testing, see appendix B). The same order of assessment was used for each visit and for each participant.

To reduce temporal perception variability (Matthews & Meck, 2014) in our experimental context, all assessments were carried out in the same research space and in the same order following a structured standard operational procedures with read out task instructions. After completion of the first visit, an appointment for a second assessment was made. Both assessments were undertaken within 72 hours of initiation of the treatment program and repeated at the end of eight weeks (last 72 hours). Participants were followed up at 12 months as part of the larger study. For the purpose of this study, only data from the first assessment round were included.

7.5.3 Measures

Gender, age, handedness, ethnicity, education, family history of substance dependence, previous admissions/counselling/therapy history, drug or alcohol usage (period of abstinence, physical complaints and craving), level of depression, self-efficacy to abstain from substance use, comorbid disorders (including comorbid symptoms severity), impulsivity,

quality of life, and the estimated level of intelligence were assessed with a self-administered demographic questionnaire, patients' medical files (intake and discharge reports), the Edinburgh Handedness Questionnaire (EHQ) (Büsch et al., 2010), the *Nederlandse Leestest voor Volwassenen* (NLV) (Schmand et al., 1992), The MATE.2.10 Outcomes Measurement (Schippers et al., 2010), Mini International Neuropsychiatric Interview version 5 (MINI 5) (Lecrubier et al., 1997), the Alcohol Use Disorders Identification Test (AUDIT) (Lundin et al., 2015), and the Drug Use Disorders Identification Test (DUDIT), (Hildebrand, 2015).

7.5.4 Neuropsychological Assessments

Motor timing was correlated with impulsivity using the Stop-Signal Task (Rapid Response Impulsivity, Band, van der Molen, & Logan, 2003) and the Iowa Gambling Task (IGT, Impulsive Choice) (Buelow & Suhr, 2009). The contribution of attention and WM to motor timing performances were assessed with regression analyses using the Corsi (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000), the Letter-Number Sequencing Task (auditory WM task LNS, WAIS –III) (Lezak, 2012) and the Stroop Colour Word Task (Attention, Lezak, 2012).

7.5.5 Motor timing: Action-Based Timing Tasks

The motor tasks consisted of a series of reaction-prediction visuo-motor pointing tasks to measure different aspects of motor timing (motor sequencing, synchronisation, and inhibition). The sequential pointing tasks were all designed by Professor Y. Delevoeye-Turrell and her team at the University of Lille, France. These tasks have been used in previous research but not SUD research (Delevoeye-Turrell et al., 2007, 2012, Dione et al., 2013, 2005; Dione & Delevoeye-Turrell, 2015). For testing, participants were seated in front of a tactile screen (Elo Touch) of 53cm by 36cm by 30 cm which was placed close to their midline in order to avoid muscle fatigue from the repetitive pointing movements. Visual and auditory signals were controlled via a PC with coded software in C++. For a detailed overview of these tasks, please see Young et al. (2016).

7.5.6 Reactivity: the motor reaction Task

When it comes to accurately executed spaced and timed reactions, subjective representation of time is crucial (Avanzino et al., 2013; Bortoletto et al., 2011; Bortoletto & Cunnington, 2010). In order to execute an interval between movements in less than a second, the complete structure of the sequence has to be planned before movement execution (Bortoletto et al., 2011). Increasing the complexity of sequencing the behaviour results in faster, movement sequences. Thus, rhythm and movement initiation are processed into an action plan before the movement occurs (Bortoletto & Cunnington, 2010). By measuring reaction and movement time abilities, whilst carrying out sub-second movement sequences in increasing complexities enabled us to measure motor planning abilities. The task used for this purpose, the Motor Reaction Task, evaluated this ability using a simple finger-pointing task to visual dots presented on the touch screen. Participants are required to lift (action initiation- measured as Reaction Time) and touch (action execution- measured as Movement Time) one dot (condition one), a series of two (condition 2) or of 3 dots (condition 3).

The manipulation of the complexity (the number of dots) of the motor sequence thus provides the means to assess lower order timing (one target) and higher order (2 and 3 dots) mechanisms through the capacity of participants to structure, organize and plan an action through time and space by ensuring accurate pointing in combination with fast movements. Condition one is designed to measure lower order mechanisms of movement initiation and execution, whereas conditions 2 and 3 were designed to measure higher order mechanisms through increased complexity, which requires structuring and planning of motor timing. Participants are instructed to start with the index finger of the dominant hand placed on the square starting zone which is situated at the bottom left edge of the screen. As soon as a black dot appears on the screen, the task is to lift of from the central target (square) and touch the target(s) as fast as possible. Three levels of complexity were counter-balanced: one target, two-target or three-target conditions. With regards to general motor timing abilities in all

participants, we expected to find decreased in motor movements with increasing sequence complexity (amount of Targets).

7.5.7 Decision-making: The Go-nogo task

In order to achieve positive outcomes in the future and function effectively, urges for immediate gratification have to be postponed and goal directed behaviour has to be given preference (Zimbardo & Boyd, 1999). To do this effectively and efficiently, cognitive control is necessary. Flexible goal-directed behaviour requires an adaptive cognitive control system for selecting contextually relevant information and for organizing and optimizing information processing. A modified version of the Go-nogo paradigm was designed to measure reaction times through a tactile touch of the touch screen. The starting zone is situated at the bottom left edge of the screen. The target is a white circle with a black letter or one-digit black number, and participants are instructed to act as fast as possible (Go) or to refrain from acting (Nogo), depending on the condition of the task. In the first condition, the task was to tap the target that appears as fast as possible (100% Go). In the following blocks, participants are instructed to react and tap the target as fast as possible also, but only if the target is a letter (50 % Go). If the target is a number, they are to refrain from reacting.

Numbers and letters were presented in semi-random order, and the targets were presented for 5s on the screen, with a random phase lag of ± 300 ms in order to avoid anticipatory responses. To assess cognitive control types, the reaction times obtained after a Go Target (of both Go (1) and Nogo (2) conditions), after a Nogo Target, and after a Nogo Target error (i.e. touched the Nogo Target) were used. Cognitive control was measured through decision making (reaction time after Go Targets and Nogo Target) and adaptability (reaction time after a Nogo Target Error). We expected cognitive control to be expressed as the measurable attempt to avoid making error, or adapting after an error has been made through faster reaction times after a Go Target compared to reaction times after a Nogo Target and a Nogo Target Error.

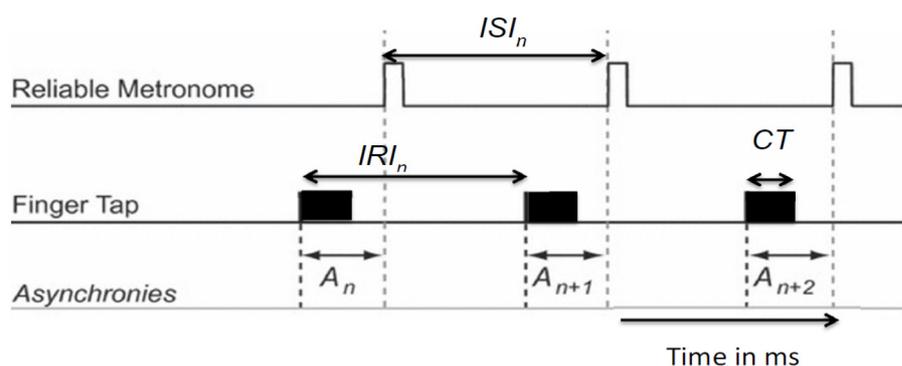
7.5.8 Synchronisation: The Spatial-tapping task

Sensory motor synchronization, defined as the ability to synchronise motor output with sensory input, offers insight into the neural mechanisms that support it, timing behaviour, and the way brain actively shapes our perception and general cognitive functioning (Iversen & Balasubramaniam, 2016). Synchronisation tasks entail finger tapping and circle drawing paradigms which measure the coordination of rhythmic movements with an external rhythm (for a review, see Repp, 2013). With our hybrid finger tapping-circle drawing task, the Spatial-tapping task (Dione et al., 2013), we aimed to evaluate how well self-initiated actions to external stimuli were timed (synchronised) in both time and space. We measured pointing accuracy in time and space as well as error in fluency and accuracy. Six black dots were presented on a tactile screen display in a circle of 100 mm apart. The instruction was to touch each target, one after the other, starting from the bottom right target, and moving counter-clockwise using the right index finger (fist closed). Each condition is constituted of a series of sixty taps of, in total, 5 trials. The total duration of the task was approximately 10 minutes, and there were two experimental conditions. A condition using the participant's own 'spontaneous' rhythm and a condition where different tempi (ISI 1100, 700, 500, and 300) were fixed in terms of inter stimulus interval (ISI in m/secs).

The ISI is considered an important independent variable in timing research (Repp & Su, 2013). In condition two, the auditory rhythm was used to pace their actions. After listening to the tones for 5.5s, participants started tapping for a total trial duration of 35s. Timing performances on this task were measured through Inter-response interval errors (IRI error), and Synchronisation errors (Asynchrony) were measured through the difference between onset of a tap and the time of onset in the external rhythm. The IRI was measured as the time intervals between the start of two successive taps and computed as the percentage of absolute difference between each IRI and the reference inter-onset interval (ISI) of a given trial. See Figure 7.1 for a visualisation of the two timing variables (IRI errors and Synchronisation errors). Spatial performances were measured through the measurement of

endpoint distributions of pointing actions and were plotted as a function of each visual target position. The mean spatial error (SE) of these spatial ellipses were used as an indication of spatial performances (Dione & Delevoeye-Turrell, 2015). The control of pauses was measured through contact time (CT) and defined as the time of finger contact with the touch screen. This measure (in m/sec) was used as an indicator of the amount of voluntary pauses in the gesture. Normal range of motor timing was expressed as poorer ability to accurately time movements at higher tempi (IRI Error), poorer ability to keep a rhythm at fast tempi (Asynchrony), more spatial errors (SE) at faster tempi and higher contact times (CT) at slower tempi.

Figure 7-1. Visual overview of Inter response interval, Inter Stimulus interval, Asynchrony and Contact



Note: IRI: Inter response interval, ISI: Inter Stimulus interval, A: Asynchrony, CT, Contact Time

7.6 Data Analyses

Backward step-wise regressions were conducted to establish the best fit of motor timing variables regarding their predictive power on EF domains of Attention and WM in motor timing performances. Best subset regressions were used to select the best fitting models, out of top 20 models, with the least number of predictor variables. For an overview of the Neuropsychological test battery, see Table 7.2. For an overview of the motor task performances, see Table 7.3.

7.7 Results

7.7.1 Sample

7.7.1.1 Demographics

All participants included in this study completed treatment. All participants were right handed, 80 percent ($n=59$) were male, and the mean age was 36.6 yrs old ($SD= 10.5$, $mode= 27$, $range 19-60$). Forty-two participants (59%) were employed, and 27 participants (36.5 %) were receiving unemployment benefits. Half of the participants were single, 13 participants (20%) were divorced and 28 participants (40%) had children.

7.7.1.2 Clinical Characteristics

Patients with comorbid disorders at treatment start were excluded from entry into the study; however, at discharge (8 weeks), some participants had been diagnosed with comorbid disorders ($n=10$, 15% Axis 1 Psychiatric disorder; $n= 15$, 20% Axis 2 Personality Disorder; $n=5$, 7% both Axis 1 and 2). Previous outpatient treatment had been attempted by $n= 38$ (51.4%), $n= 23$ (31%) had received psychotherapy, 12 participants (16.2%) had previously been admitted to psychiatric inpatient care (non SUD-majority due to a failed suicide attempt), and for 21 participants (29%), this was the second (or more) attempted inpatient rehabilitation. Upon admission, 23 (31%) of the participants had a positive alcohol test (through Breathalyzer examination), and 38 participants (54%) had a positive drug test (Cocaine $n=25$ (33%), Benzodiazepine $n=8$ (10.8%), Cannabis $n=5$ (6.8%), and Amphetamine $n=1$ (1.4%). Drug use other than Cocaine and/or Alcohol was minimal, with 9 percent using Methylenedioxymethamphetamine, other stimulants (e.g. Speed, Methamphetamine 15 percent) and Sedatives (prescription 12 percent) in the 30 days before admission to treatment. For 22 participants (30%), detoxification prior to admission to the clinic was necessary. Comorbid psychiatric symptoms were below the clinical threshold on the Anxiety, Depression

and Stress scale (MATE Q2 total score of < 60) ($M= 41.8$, $SD= 25.2$, $mode=12$). Craving symptoms were minimal at baseline (MATE Q1 total scores of <12) ($M= 7.5$, $SD= 3.9$). A detailed overview of the described clinical measures can be found in table 7.1.

Table 7-1. Clinical and demographic characteristics of all participants

	All patients	
	<i>M</i>	<i>SD</i>
<i>N</i> =74		
Age	37.1	11.1
Alcohol Use last 30 days	13.1	10.3
Alcohol quantity used last 30 days (units)	12.6	12.3
Cocaine Use last 30 days	8.8	10.4
Cocaine quantity used last 30 days (grams)	1.5	2.5
AUDIT	19.6	10.7
DUDIT	23.6	13.2
Sheehan	18.6	7.8
Duration of Use	17.3	10.3
Age of first Use	19.6	6.8
Abstinence in days	14.9	12.2
GAF score at admission	52.3	8.9
Physical Complaints	11	7.6
Craving (last 30 days)	7.5	3.9
Comorbid Symptom Severity	20.9	12.6

Note. Results of separate groups; IQ: *Nederlandse Leestest voor Volwassenen* indication of intelligence, AUDIT: Alcohol Use Disorder Identification Test, DUDIT: Drug Use Disorder Identification Test; Quality of Life, Sheehan Disability Scale (SDS), Impulsivity, (BIS) Behavioural Inhibition Scale; GAF: Global Assessment of Functioning. MATE 5 Measurements in the Addictions for Triage and Evaluation, Physical Complaints/health related symptoms in the last 30 days; MATE Q1, Measurements in the Addictions for Triage and Evaluation, Craving Scale regarding the last 30 days; MATE Q2, Measurements in the Addictions for Triage and Evaluation, Anxiety, Depression, Stress Scale last 30 days.

Table 7-2. Neuropsychological test results

All Participants (N=74)

Attention			<i>M</i>	<i>SD</i>
STROOP	Attention	Congruent	784.6	175.6
		Incongruent	974.7	214.5
Working Memory				
CORSI	Visual Working Memory		4.9	.7
LNS	Auditory Working Memory		11.4	2.9
Impulsivity				
IGT	Impulsive Choice		55.4	18.1
SST	Rapid Response Impulsivity		273.2	107.2

Note. Stroop task; classical stroop task with congruent (e.g. word blue in blue font) and incongruent (e.g. word blue in red font), Corsi; visual working memory task, LNS; Letter Number Sequencing Task, auditory working memory, IGT; Iowa Gambling Task, Impulsive Choice, SST; Stop Signal Task, Rapid Response Impulsivity.

7.7.2 Main results: executive functioning and motor planning

7.7.3 Impulsivity

Motor timing abilities were correlated with Impulsive Choice (IGT) and Rapid Response Impulsivity (SST) and performance the three motor tasks (Motor Reactivity, Go-Nogo and the Spatial-tapping task). No significant correlations were found between any of the motor task performances and Impulsive Choice and Rapid Response Impulsivity.

7.7.4 Working Memory

7.7.4.1 Auditory Working Memory

A best subset regression analysis showed that auditory WM performances explain a small part of the variance occurred in motor timing performances ($R^2=17$). With regard to Motor reaction task, Auditory WM is a significant predictor with regard to the 3 Target Conditions on Reaction Time ($b= -.28$, $t(62) = -2.39$, $p=.02$) and Movement Time ($b= .29$, $t(62) = 2.39$, $p=.02$).

7.7.4.2 Visual Working Memory

A best subset regression analysis showed that visual WM performances explained a small portion of the variance occurred in Motor Timing performances ($R^2=17$). With regard to Motor reaction task, visual WM was a significant predictor with regard to Movement Time in the 3 Target Condition ($b= .38$, $t(62) = 3.27$, $p<.01$). Visual WM was a significant predictor in Asynchrony performances at ISI1100 ($b= -.27$, $t(62) = -2.41$, $p<.02$) and SE at ISI300 ($b= -.29$, $t(62) = -2.56$, $p<.01$).

7.7.5 Attention

A best subset regression analysis showed that performances on the Incongruent Condition of the Stroop task explained a small portion of the variance in motor timing

performances ($R^2=16$). Attention was a significant predictor of spatial abilities on ISI1100 ($b=.31$, $t(55) = 2.48$, $p<.01$).

7.8 Discussion

This study did not find any associations between Impulsive Choice and Rapid Response Impulsivity and motor planning, decision making and synchronisation abilities. This is in line with previous research indicating that stimulant dependent individuals exhibit motor timing deficits that cannot be explained by cognitive deficits (Wittmann et al., 2007). Auditory WM predicted motor timing, but only on the Motor reaction tasks conditions measuring higher order timing mechanisms. Thus, auditory WM only predicted motor timing when structuring and planning of motor timing was required. Visual WM was also predictive of motor timing performances. Like auditory WM, visual Wm was predictive when structuring and planning of motor timing was required. Visual WM was, however, also predictive when cognitive load demands increased in synchronisation performances (at tempo extremities ISI 1100 and ISI 300). Specifically, the ability to time the tone correctly at very slow tempi and spatially when the tempo was very fast. Attention was only predictive of spatial abilities on very slow tempo trails. Based on these findings, and in line with the literature, timing should be considered as an independent process (Arce & Santisteban, 2006; Pine et al., 2010). Deficits in attention and working memory are thought to impair the ability to plan ahead and consider all information available before choices are made without considering all alternatives (Arce & Santisteban, 2006).

Timing deficits have been associated with attention and working memory. A number of human timing studies have indicated that sustained attention and working memory are crucial in accurate estimations of intervals in the seconds range (Wittmann et al., 2007). However, this may only affect motor timing abilities of longer (than one second) intervals and not millisecond timing. We found that millisecond timing performances were not related to impulsivity. They are, however, associated with WM demands and attention. We, therefore,

argue that in line with the literature (Jennifer T Coull et al., 2011; Ivry & Spencer, 2004), motor timing should be considered as an independent process and be evaluated further in studies of SUD, with timing confounds considered in neurocognitive and treatment outcome paradigms (Jennifer T Coull et al., 2011). A limitation of this study is that our tasks measure motor timing performances in the millisecond range only, and cognitive processes such as attention, WM and Impulsivity might not be recruited as much at these time spans compared to longer intervals. We encourage future research to repeat these test paradigms with longer time intervals to delineate the significance of interval durations on the recruitment of cognitive functions.

7.9 References

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8 Conclusion, Study Limitations and Directions for Future Research

8.1 Conclusion

This study sought to extend the motor timing literature evidence base by contributing data that enhances our understanding of the mechanisms that play a central role in SUDs. Below are the general conclusions and discussion of the study results, followed by the limitations of the study and recommendations for future research

8.1.1 Prognostic value of motor timing in SUD treatment outcomes

A main aim was to test the theoretical basis for prognostic indicators in SUD with regards to motor timing (measured in terms of treatment response and relapse). We expected that motor coordination and planning abilities, synchronisation abilities and decision making would be prognostic of treatment outcomes (self-perceived efficacy to abstain from substances) at 8 weeks and relapse at 12 months (yes/no). Due to a very small portion of the original sample reached for follow-up, the analyses of motor timing variables with regard to relapse at 12 months' were omitted. With regard to treatment outcomes we found that motor timing variables explained 27 percent of alcohol use self-efficacy, and 25 percent of cocaine use self-efficacy at discharge. With regards to alcohol self-efficacy, Spatial Errors (at ISI 300), Asynchrony (at ISI 400) and Inter Response Interval Errors (at ISI 500 and 700) were predictive of self-perceived self-control to abstain from alcohol use. With regards to cocaine self-efficacy, Spatial Errors (at ISI 300 and 500) and Contact Time (at ISI 300) were predictive of self-perceived self-control to abstain from cocaine use. Interestingly the motor timing variables predicting cocaine and alcohol self-efficacy were not the same. This may indicate that there are different factors at play in different SUDs. The timing variable that is shared by both alcohol and cocaine self-efficacy, and both at high tempi only, is spatial error. Interestingly, when patient performances were compared (see chapter 6) patients outperformed HC on spatial abilities. In light of the fact that patients performed significantly worse on most other timing variables assessed, this is an interesting finding. A search of the

literature did not give us a possible explanation for these seemingly conflicting findings. However, we argue here that these findings could point to compulsivity in patients. Spatial abilities rely heavily on visual feedback and patients may choose to be accurate above being correct. With this we mean that the patients have shown to be significantly less able to tap in time and keep a rhythm at tempo extremities (very fast or very slow tempi). However, they are consistently more accurate than HC. This could point to high compulsivity levels in patients. What the predicting variables also have in common is that they are all at high tempi. This again, as pointed out throughout the work point to deficits only coming to light when the patient is under pressure. When cognitive load goes up, which is the case when time constraints are present, the deficits become apparent.

8.1.2 Support for the model of van Hoof

A main aim of this study was to indirectly test for imbalances in the DM and GM as proposed by the model of van Hoof (2002; 2003). Previous research using these motor tasks has shown motor planning, spontaneous movement variability, and synchronisation variability in populations with Schizophrenia compared to HC (Delevoeye-Turrell et al., 2007, 2011). Based on this research, hypotheses were formed to indirectly find support for the model of van Hoof (2002; 2003) regarding dual circuitry imbalances SUD populations.

Three out of six Hypotheses in support of a stronger DM comparatively to the GM were supported. (i) The hypothesis stating that higher internal clock rate (higher spontaneous rhythms on the Spatial-tapping task [Task 2]), would reflect a stronger DM was not found in patients and HC group comparisons. Furthermore, the hypotheses that lower motor coordination and planning (higher reaction times and lower movement times on the Motor reactivity task [Task 1]) would reflect a stronger DM was not found. As such, self-initiated rhythms and motor planning did not differ between patients and HC. A third hypothesis stating that lower inhibitory capacities (higher reaction times on the Go stimuli in

the No-go trail and more errors on the Nogo stimuli in the Nogo trail [Task 3]) in SUD individuals compared to HC, indirectly indicate a stronger DM relative to the GM, was supported. Specifically, patients had faster reaction times on Go trails and after Nogo Errors were made, an indication for poorer decision making, or motor control abilities in SUD populations. This indirectly supports the notion of a stronger automatic, DM, relative to reflective GM.

With regard to individual differences in patient groups only hypotheses with regard to a stronger DM (relative to the GM) were made. Future research should include hypotheses on GM also. We hypothesised that the alcohol group would be more sensitive to negative feedback and as a result, a decrease in performance was expected as a result of errors on a speed performance tasks (Go-nogo Error [Task 3]), and, that comparatively lower inhibitory capacities in the CUD group compared to the AUD group (Go-nogo [Task 3]) would be found. The latter was supported by the data. We found that the CUD group reacted significantly faster than the AUD group. That the alcohol group would be more sensitive to negative feedback was not supported by the data. No differences in reaction times after a Nogo Error were found between the patient groups.

With regard to a weaker GM relative to the DM decreasing the ability to make internal representations, we hypothesised to find lower synchronisation abilities (the spatial-tapping task trails that are at higher tempi [Task 2]) in addicted individuals compared to HC. This was supported by the data. We found that at ISI 1100 patients performed significantly worse compared to HC. The patients were less able to make accurate predictions at slower tempi and thus more errors synchronising their movements when predictions had to be made.

The data supports the model of van Hoof on the assumption that that patients with SUD make faster decisions compared to HC. Additionally, they are worse at inhibiting responses in order to adapt, or increase motor control, after errors are made (e.g. slow down reaction times to avoid further Nogo Errors). Not only do they have trouble adjusting after errors are made, there is hardly any differences between Go and Nogo trails with regard to

reaction times. Interesting finding is that patients speed up considerably after they made errors (see table 6-2 for patient means on Go, Nogo and Nogo Error trails). This is an interesting finding since there seems to be an element of 'loss of control' once Errors are made. Based on the small differences between reaction times after Go trails and Nogo trails, and the speeding up of reaction times after Nogo Errors are made, leads us to suggest that there is indication of a stronger DM, but only at increased cognitive loads. The data does not support the model of van Hoof that individuals with SUD would have faster spontaneous rhythms, and deficits in planning and coordination of movements. These findings could be explained by the fact that the DM is largely intact in SUD populations, or, the findings may be accounted for by the lack of increased cognitive load on these tasks. The results of every chapter highlight the finding that deficits found, DM, GM, or otherwise, were only visible when cognitive load was significantly increased (i.e. asynchrony at slow tempi, IRI at fast tempi, elevated reaction times after errors were made). It may be that stress is a mediator, and indirectly affects the automatic DM and puts pressure on the reflective GM. This could explain the results found and why no results were found on the tasks that had no performance pressure (spontaneous rhythms, motor planning and coordination). Asking a participant to touch targets at their own chosen speed, and carry out sequential movements (planning and coordination) may not be enough to tease out possible deficits in the dual circuitry model proposed by van Hoof (2002; 2003).

8.1.3 Motor timing outcome differences between patients

A main aim was to assess recovery in motor timing abilities and individual differences between AUD and/or CUD groups. Specifically, we compared timed motor coordination and planning (Motor reaction task [Task1]), decision making (Go-nogo Task [Task3]) and synchronisation abilities (Spatial-tapping task [Task2]), at baseline, and discharge (week 1 and 8), in three groups (a group with AUD, a group with CUD, and a group with both AUD and

CUD). We hypothesized that at 8 weeks, motor coordination and planning abilities (Motor reaction task [Task 1]) would improve at post-treatment for all patient groups. This was not supported by the data. We did find that the alcohol group had the lowest overall movement initiation times (Reaction Times) whilst the CUD group had the highest. Only the CUD group significantly improved on movement initiation and execution times, and only on condition 2 (2 targets) which could indicate a possible recovery in motor planning abilities in this group. Additionally, we hypothesised that increased decision making abilities would be found. This was not supported by the data. There were no differences in decision making abilities and no recovery or increased abilities were found at discharge. Lastly, we expected improvement in all patient groups in synchronisation abilities through; (i) lower synchronisation errors and (ii) inter response interval errors, (iii) lower contact times and, (iv) lower spatial error rates. These hypotheses were supported by the data. Both rhythmic abilities and synchronisation with external events, as well as spatial abilities, improved with prolonged abstinence. Keeping in tune with a rhythm (IRI) was harder at faster tempi for all patients at the start of treatment compared to after treatment. However, only the CUD group improved significantly. Additionally, poorer synchronisation abilities were found at treatment start and more so at slower tempi. These performances did improve over time only significantly so for the AUD group. With regard to spatial abilities, improvements were only found for the AUD and CUD groups, but not the AUD/CUD group in SEs. The SE rates for all individuals were lower at discharge compared at admission. The CT was longer at slower tempi for all participants but did not change over time and was similar for each group. Leading from this, it can be suggested that the improvements observed on both movement initiation and execution and interval timing, in time and in space, might correspond with the recovery of cognitive abilities in CUD and/or AUD. Interestingly the CUD, AUD and CUD/AUD groups did not all recover equally. Research on neurocognitive deficits in SUD is in line with this finding in that not all SUD cause the same deficits and differences between substances used may cause differences in recovery length and severity of symptoms (Bates, Bowden, et al., 2013; Bates et al., 2002; Bolla, Funderburk, & Cadet, 2000; Walvoort et al., 2013)

8.1.4 Motor Timing, Attention, Working Memory and Impulsivity

With regard to our secondary aims, we found good test retest reliability for the motor tasks showing that this battery was reliable to use in studies that use repeated measure methods of the assessment of motor timing. Furthermore, we found that impulsivity did not correlate with motor timing performances in SUD. Motor timing research in SUD is scarce, but our result seems to be in line with previous research which found that motor timing was not explained by impulsivity (Wittmann et al., 2007). However, there is clearly little consensus on this topic and more motor timing research in SUD is needed to create a clearer picture on this finding (Brighthouse et al., 2013; JT T. Coull & Nobre, 2008; Falter & Noreika, 2011; Noreika et al., 2013; Pine et al., 2010; Wittmann et al., 2007). Additionally, attention and working memory only partially contributed to motor timing in patients with SUD. These findings suggest that that motor timing abilities could be considered separately to other cognitive domains, at least in SUD. However, this is the first study of its kind, and more research is needed to make statements about the possible implications of these findings. A possible explanation could be that no correlation was found between impulsivity and motor timing because all patients were highly impulsive and there was little variability in the results, or not enough to show significant correlations. The fact that we did find motor timing differences in HC subjects (Chapter 3) leads us to believe that there may be confounding factors at play and that further research may disprove our findings.

8.1.5 Limitations of the study

One limitation of the study was that only participants without comorbid disorders, who did not use psychotropic medications, were included in the study, in order to avoid the confounding effects of comorbid psychopathology and the effects of psychotropic medications on performance. This significantly reduces the generalisability of the findings

and results should be interpreted with care. Reality is that most patients admitted to inpatient rehabilitation do have a comorbid disorder and most will take psychotropic medication at some point. Additionally, even though patients that presented with a comorbid disorder at treatment admission were excluded, there was still a significant amount of patients that were diagnosed during treatments. This poses further questions about generalisability of the results; is it the comorbid disorder that mediated the results? Another limitation is that these patients were in treatment for a period of 8 weeks. During this period, they did not have access to their phones, ate healthily, exercised, and had a generally structured and supported lifestyle. There were no 'crisis situations' such as one would expect in real life or outpatient treatment centres. This 'stability' of environment could have influenced the results obtained. Research attempting to replicate the results in outpatient populations may shed light on this possible limitation. The sample size of the follow up was disappointingly small, a shorter time to follow up may result in a larger follow up sample. Also the method of follow up is prone to confounding results. A telephonic interview may tempt patients to not be truthful about their drug use. Structured interviews in person, perhaps including a urine test may yield a more solid result.

Future research should focus on more diverse populations with SUD, inpatients and outpatients and at different point of recovery. In terms of future directions, a number of interesting questions arise in the context of motor timing, cognitive load, and high impulsivity. For example, does impulsivity only affect motor timing when a certain cognitive load is reached? If there is a link between reduced motor control and high levels of impulsivity, is this relationship mediated by a greater cognitive load? While it may be hypothesized based on the results of the study that this is the case, more research on impulsivity in non-clinical populations is needed (Hamilton, Littlefield, et al., 2015; Moreira et al., 2016).

The novel findings of this study suggest that further scrutiny of the deficits implicated in impulsivity in healthy populations is warranted. Contrary to much of the impulsivity literature, we did find elevated reaction times in line with research (for a review, see Arce &

Santisteban, 2006) but only on tasks that involved performance (such as performance under time constraints). We did not find elevated reaction times on tasks that did not also measure performance in some other way. This question may be interesting to pursue with further research. Interestingly, we found no correlation between patient motor timing performances and impulsivity (IC and RRI). This inconsistency with the existing literature may, in part, also be due to variations in specificity of the impulsivity construct and the measurement tools used to assess impulsivity (Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015). In light of these findings, we argue that specificity of timing deficits and impulsivity (Hamilton, Littlefield, et al., 2015; Hamilton, Mitchell, et al., 2015; Wittmann & Paulus, 2008) and their contribution to the aetiology of psychiatric disorders (Cyders, 2015) require further investigation.

Furthermore, timing deficits found in this study, across analyses, are present, but only when cognitive load was increased. A possible explanation for the association between cognitive load and motor timing abilities in SUD patients and highly impulsive individuals in the HC group suggests that time constraints and errors may be perceived as (more) stressful; they also increase (perceived) cognitive load and subsequently lead to loss of control over inhibition and rhythmic abilities. To our knowledge, this is the first study to demonstrate such an association, and based on our findings, replication studies on motor timing abilities in SUD samples, their prognostic value and their specificity for different SUD, are warranted.

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Appendix A Neuropsychological assessment

PROCEDURE NEUROPSYCHOLOGISCHE TESTS (NL)

Om de Neuropsychologische batterij te beginnen: -

Alle instructies voor de taken zullen voorgelezen worden net als nu. Dit wordt gedaan omdat het belangrijk is dat de instructies voor iedereen gelijk zijn. Door de instructies voor te lezen zorgen wij hiervoor. We gaan een aantal neuropsychologische taken doen die ontworpen zijn om de functie van het brein en het zenuwstelsel te meten. Bij de taken moet je vragen beantwoorden en dingen met je handen doen. De taken testen geheugen, probleem oplossen, concentratie en motorische vaardigheden. Sommige van de taken zijn makkelijk en zijn zo ontworpen dat iedereen er goed op kan presteren. Andere taken echter, zijn zo ontworpen dat er tijdens de taak een punt komt waarop je niet langer goed kan presteren. De taak is dan te moeilijk. Je zal niet goed zijn in *alle* taken – dat is namelijk niemand! De taken zullen bij elkaar ongeveer 1 uur duren. Je mag het me altijd zeggen als behoefte hebt aan een pauze.

STOP SIGNAL TASK

Gecomputeriseerde taak. Uitleg Stop Signal Experiment:

“In het midden van het scherm verschijnt steeds een groene pijl.

Als de pijl naar rechts wijst, druk dan zo snel mogelijk met je rechterhand op de rechter knop. [/]

Als de pijl naar links wijst, druk dan zo snel mogelijk met je linkerhand op de linker knop. [z]

Soms wordt de pijl plotseling rood: probeer dan niet op de knop te drukken.

Het zal niet altijd lukken om je reactie te stoppen, je hebt dan al gedrukt voordat je ziet dat de pijl rood is geworden. Maar het is belangrijk dat je altijd zo snel mogelijk reageert, en dus niet gaat wachten of de pijl rood wordt. De computer is zo ingesteld dat het stoppen de helft van de keren lukt en de helft van de keren niet.

Ga dus niet wachten of de pijl rood wordt maar reageer altijd zo snel mogelijk.

We beginnen nu eerst met een kort oefenblok. Daarna kun je vragen stellen, wanneer iets niet duidelijk is. Na een korte pauze begint de echte taak. Deze bestaat uit 3 blokken.

Samenvatting:

Je opdracht is:

1. Druk zo snel mogelijk op de rechter knop wanneer de pijl naar rechts wijst.
2. Druk zo snel mogelijk op de linker knop wanneer de pijl naar links wijst.
3. Druk niet als de pijl rood wordt.
4. Het is heel belangrijk om niet te gaan wachten of de pijl rood wordt. Het is heel belangrijk om steeds zo snel mogelijk te blijven reageren. Onthoud dat iedereen fouten maakt bij het proberen stoppen: de taak is zo ingesteld dat het ongeveer de helft van de keren lukt en de helft van de keren niet lukt.”

CORSI

Gecomputeriseerde taak: de instructies staan – in het ENGELS - op het scherm.

Nederlandse vertaling:

“Je gaat nu een taakje doen dat test hoe goed je een volgorde van locaties op het scherm kunt onthouden. Je zult 9 blauwe vierkanten op het scherm zien. In elke trial, zullen de vierkanten één voor één oplichten in een bepaalde volgorde. Onthoud die volgorde. Wanneer de sequentie klaar is, moet je op de vierkanten klikken IN DEZELFDE VOLGORDE ALS WAARIN ZE WAREN OPGELICHT. Als je klaar bent, klik dan op ‘DONE’ onderin het scherm. Als je de volgorde van de vierkanten niet meer kan herinneren, probeer dan de vierkanten aan te klikken op een manier die zo veel mogelijk lijkt op de originele volgorde.

Je zult beginnen met een sequentie van 2 vierkanten, en je krijgt 2 pogingen voor elke sequentie lengte. De sequentie zal steeds één langer worden wanneer je tenminste één van die twee pogingen goed hebt.

Je zal nu eerst 3 oefentrials doen om bekend te worden met de test. Deze oefentrials zullen niet je score beïnvloeden.

Na de oefentrials: **Nu zul je de normale trials doen. Deze zullen meetellen voor je score op deze test.**

STROOP TASK

Gecomputeriseerde taak: de instructies staan op het scherm. Lees deze instructies hardop voor.

VOEG TOE:

- **het is belangrijk dat je naar het scherm blijft kijken.** (fixatiepunt)
- **Het is belangrijk om de positie van de kleurtoetsen te onthouden, omdat je dan beter in staat bent om snel te reageren. Als je niet steeds naar het toetsenbord hoeft te kijken waar de kleuren waren, scheelt dat namelijk tijd.**

IOWA GAMBLING TASK

Gecomputeriseerde taak: de instructies staan op het scherm. Lees deze instructies hardop voor.

Maak goed duidelijk dat ze op zoek moeten gaan naar de ‘goede stapels’, en dat het ook echt mogelijk is om te ontdekken welke stapels dat zijn.

LETTER NUMBER SEQUENCING

Ik ga zometeen een aantal letters en cijfers noemen. Nadat ik ze heb gezegd, wil ik dat je eerst de cijfers opnoemt. Doe dat op volgorde en begin met het laagste getal. Noem daarna de letters op alfabetische volgorde op. Bijvoorbeeld, als ik zeg B – 7, zou je moeten antwoorden 7 – B. Het cijfer eerst, dan de letter. Als ik zeg 9 – C – 3, zou je moeten antwoorden 3 – 9 – C. De cijfers op volgorde eerst, dan de letters op alfabetische volgorde. Laten we even oefenen.

6 – F (6 – F)
G – 4 (4 – G)
3 – W – 5 (3 – 5 – W)
T – 7 – L (7 – L – T)
1 – J – A (1 – A – J)

Als de proefpersoon een fout maakt op een oefen-item, corrigeer hem/haar en herhaal de instructies als dat nodig is. Ook als de proefpersoon alle oefen-items fout doet, ga dan verder met de subtest.

Één letter of cijfer per seconde opnoemen

Dat is goed. Dan gaan we nu beginnen met de echte taak.

Noem de sequenties van het scoreformulier en geeft de juiste scores voor iedere trial. Als de proefpersoon *alle 3 de trials* van een item 0 scoort → stoppen met de taak.

TRAIL MAKING TEST

Trails A:

Voorbeeld: “**op deze pagina staan een aantal getallen (wijs aan). Begin bij nummer 1 (wijs naar 1) en teken een lijn van 1 naar 2 (wijs naar 2), 2 naar 3, (wijs naar 3) 3 naar 4, (wijs naar 4) enzovoort, totdat je het einde bereikt (wijs naar de cirkel gemarkeerd met end). Teken de lijnen zo snel als je kan. Ben je er klaar voor? Begin!**”

“Goed! Laten we de volgende proberen.” (als er geen problemen zijn, ga naar Test)

Als de proefpersoon een fout maakt bij SampleA, wijs dan op de fout en leg het uit. De volgende verklaringen van fouten dienen ter illustratie:

“Je begon bij de verkeerde cirkel. Dit is waar je moet beginnen” (wijs naar nummer 1)

“Je hebt deze cirkel overgeslagen (wijs naar de overgeslagen cirkel). **Je moet van nummer 1** (wijs) **naar 2** (wijs), **dan naar 3** (wijs), **enzovoort, totdat je de cirkel bereikt die aangegeven staat met ‘end’.** **Sla geen nummers over maar ga van de ene naar de andere in de juiste volgorde. Denk eraan dat je dit zo snel als je kunt moet doen. Ben je er klaar voor?.. Begin!**

Test: **“op deze pagina staan nummers. Doe dit op dezelfde manier. Begin bij nummer 1** (wijs naar 1) **en teken een lijn van 1 naar 2** (wijs naar 2), **van 2 naar 3** (wijs naar 3), **van 3 naar 4** (wijs naar 4), **enzovoort, op volgorde totdat je het einde bereikt** (wijs naar de cirkel die gemarkeerd staat met end). **En denk eraan: doe dit zo snel als je kan. Ben je er klaar voor?.. Begin!**

Houd bij hoe lang de proefpersoon erover doet om de taak tot een einde ten brengen (in seconden)

Tijdlimiet = 96 seconden.

Als de proefpersoon een fout maakt, wijs hem/haar er dan meteen op en laat hem/haar weer teruggaan naar de plek waar de fout gebeurde. **“Je hebt een cirkel overgeslagen. Ga terug naar”** (laatst correcte cirkel). Stop niet met de timing.

Na afronding van Trails A Test, zeg: **“Dat is goed. Nu zullen we een andere proberen”**

Trails B:

Sample: **“We zullen nu iets anders proberen. Op deze bladzijde staan nummers** (wijs) **en letters** (wijs). **Je wordt nu gevraagd om een lijn te tekenen, afwisselend van nummer naar letter. Begin bij nummer 1** (wijs naar 1) **en teken dan een lijn van 1 naar A** (wijs naar A) **van A naar 2** (wijs naar 2)

van 2 naar B, (wijs naar B) enzovoort, totdat je het einde bereikt (wijs naar de cirkel gemarkeerd met end). Teken de lijnen zo snel als je kan. Ben je er klaar voor?... Begin!

“Goed! Laten we nu de volgende proberen” (als er geen problemen zijn, ga naar Test)

Test: “Op deze pagina staan nummers en letters. Doe dit op dezelfde manier als net. Begin bij nummer 1 (wijs naar 1) en teken dan een lijn van 1 naar A (wijs naar A) van naar 2 (wijs naar 2) van 2 naar B, (wijs naar B) enzovoort, totdat je het einde bereikt (wijs naar de cirkel gemarkeerd met end). En denk eraan: doe dit zo snel als je kan. Ben je er klaar voor?... Begin!

PROCEDURE NEUROPSYCHOLOGISCHE TESTS (ENG)

To begin the Neuropsychological Battery: -

- All the instructions for the tasks will be read out like this.
- By reading out the instructions we make sure that the instructions are the same for everyone.
- We will do a number of neuropsychological tasks that are designed to measure the brain and nervous system functioning.
- You will need to answer questions and use your hands
- These tasks test memory, problem solving, concentration and motor skills.
- Some of the tasks are easy and you will be able to perform well.
- Other tasks, however, are designed so that they become increasingly difficult.
- During the task you will reach a point where you can no longer perform well.
- The task becomes too difficult.
- No one will be good at all the tasks.
- These tasks will take approximately 1 hour.
- You can always tell me if you need a break.

STOP SIGNAL TASK

Computerized task. Explanation Stop Signal Experiment:

Evaluator info: Neuropsych tasks- use this version

-green arrows

-new subject-month, date, year-

code subject-txt)

(Mouse double left click to move between tasks, ESC x2)

.

In Summary:

In the middle of the screen, a green arrow will appear.

Remember:

1. To press the right button with your right hand when you see an arrow pointing right.
2. To press the left button with your left hand when you see the arrow pointing left.
3. ***Do not*** press when the arrow is red.
4. It is very important not to wait whether the arrow is red.
5. It is very important to always respond ASAP.
6. Sometimes you would already have pressed a button before you see that the arrow has become red.
7. But it is important that you always respond as quickly as possible, and not wait to see if the arrow will turn red.
8. Remember that everyone makes mistakes when trying to stop.
9. The task is set so that half of the time you will succeed and half the time you will not.
10. We will begin with a short training block to make sure that you understand the task.
11. Then you can ask questions if something is not clear.
12. After a short break, the real task will begin which consists of three blocks.

CORSI

Computerized task, the instructions are - in ENGLISH - on screen.

Evaluator info:

Move keyboard-Pebl battery corisi-subject code- participant code-run test-adjust screen-close by itself)

You will be given a task that:

1. Measures how well you can remember a the order of a sequence.
2. On the screen you will see nine blue squares.
3. In each trial, the squares will light up yellow one by one in a certain order.
4. Please remember that order.
5. Then you need to click on the squares in the same order as they were illuminated.
6. Then when you have completed your selection, click "DONE" at the bottom.
7. If you cannot remember the order of the sequence, try to click as close as possible to the original sequence.
8. You will begin with two squares and you will get two attempts for each sequence length.
9. Each time you have a sequence correct, a square will be added to the sequence.
10. First you will do 3 practice trials to get familiar with the test.
11. These practice trials will not affect your score.
12. After the practice trials, you will begin the normal trials which will count towards your score.

Dutch translation:

STROOP TASK

Computerized task: the instructions on the screen. Read these instructions aloud.

Evaluator info: (end only-purple-4th one)

(Trial: Ctrl alt delete enter if want to get out)

You will be given a task that:

1. You will have to identify the following colours: red, blue, green and yellow.
2. You will see words on the screen and will have to identify what colours they are.
3. Please place your fingers on the buttons that have been allocated for the colours.
4. Right hand, red and blue. Left hand yellow and green.
5. It is important that you keep looking at the screen and not at your fingers..
6. There will be a practice round to help you remember the position of the color keys because you are then better able to respond quickly.

IOWA GAMBLING TASK

Computerized task: the instructions on the screen. Read these instructions aloud.

Evaluator info: NL Bianca

1st one-session 1abcd

2nd one-session 1 cdba-

enter-reuse empty cards- enter

Space bar during instructions, enter to begin task. Esc to exit.

You will be given a task that:

- 1. Is a gambling task, where you need to try and win as much money as you can.**
- 2. You will see there are 4 piles of cards labelled A, B, C & D.**
- 3. On the keyboard you will see corresponding letters, please push these when you wish to choose a card pile.**
- 4. The aim is to find out which piles are 'good piles' to win as much money as you can.**

LETTER NUMBER SEQUENCING (Susanne)

You will be given a task where:

- 1. I will call out a number of letters and numbers.**
- 2. Then I would like you to first say the numbers in order from lowest to highest.**
- 3. Then place the letters in alphabetical order.**
- 4. For example, if I say B - 7, you would have to answer 7 - B.**
- 5. First the number, then the letter.**
- 6. When I say 9 - C - 3, you would have to answer 3-9 - C.**
- 7. Please remember to put the numbers in order from lowest to highest and the letters in alphabetical order.**
- 8. Let's practice.**

6 – F	(6 – F)
G – 4	(4 – G)
3 – W – 5	(3 – 5 – W)
T – 7 – L	(7 – L – T)
1 – J – A	(1 – A – J)
- 9. In the practice items, if the subject makes an error, then please correct him / her and repeat the steps as often as needed.**

10. Even if the subject in training does all items wrong, then proceed to the test.

11. That is good. Then we begin the real task.

12. List the sequences of the score sheet and give the correct scores for each trial.

13. The subject has 3 trails of an item, thereafter score 0 for the task.

TRAIL MAKING TEST

You will be given a task that:

1. You will have to use a paper and pen.

2. You need to draw a line without lifting your pen from the paper from the lowest to the highest number.

3. We will begin with Trail A (lowest to highest number)

- **Example:** "On this page are some numbers (point out). **Start with number 1** (point to 1) **and draw a line from 1 to 2** (point to 2), **2 to 3** (point to 3) **3 to 4** (point to 4) **and so on until you reach the end** (point to the circle marked end). **Keep your pen on the paper. Draw the lines as fast as you can. Are you ready? Begin! "**

- *(Let them do it to practice).*

- If the subject makes an error in Sample A, assign the error and explain. The following statements from mistakes serve to illustrate:

"**You started with the wrong circle. This is where to start** "(point to number 1)

"**You've missed a circle** (point to missed circle). **You should connect number 1** (point) **to 2** (point), **then to 3** (point), **and so on, until you reach the circle marked state with 'end'**. **Do not skip numbers. Remember to do this as fast as you can. Are you ready? .. Start! Keep track of the time using a stopwatch how long it takes for the subject to complete.**

Time Limit = 96 seconds. Time their reaction time and write it on the page.**4. Trial B:**

After completing Trails A Test, say, "**That's great. Now we will try another one** "

Trial B

- **Example:** "**We will now try something else. On this page are numbers** (point) **and letters** (point). **You will be asked to draw a line from number to letter a line. Starting with number 1** (point to 1). **Then draw a line from 1 to A** (point to A) **Then from 2** (point to 2) **to B** (point to B) **and so on until you reach the end** (point to the circle marked end). **Draw the lines as fast as you can. Are you ready? ... Begin!**

"**Good! Let's do the test** "

Appendix B Motor timing task instructions: Dutch and English

To set up:

- Start laptop
- Start Archlinux program
- Password: Jacques52
- Open Matlab
- Matlab instructions;
- Top bar open “Vanhoof-v6” folder
- Press “actionplanning.m”
- Press green arrow “play” (top task bar)

Options used in MATLAB:

- 1= Screen Calibration
- 2=RTMT
- 3=Flexstab
- 5=Selective Reaction Time
- 6= end programme

To begin Motor task assessments:

- Press 1 for screen calibration
- If you make a mistake press escape to exit.
- Go back to editor ‘main folder’ and press green arrow “play” again
- Leave editor and use T2 if you want to re-run a specific task.
- Choose what task to run

Task instructions for examiner:

- For the entire experimental session, subjects are seated on a stable chair.
- The screen is positioned at knee height in between the subject's legs.
- Subjects need to sit with a straight back and need to be able to touch the far side of the screen, with arms stretched out in front of them.
- The middle of the screen ("ELOTOUCH" symbol) must be aligned with the subject's midline.
- Importantly, subjects must adopt a comfortable position.
- Subjects must not change in between conditions of a given task.

!! Please ensure that you are not giving away/tell the participant the expected outcome of the research -which is that we expect addicted individuals to perform worse than healthy participants- as this will create bias, make the participant feel uncomfortable and, confound the results.

Task instructions for participant:

The instructions (in italics below) are read as an introduction to the motor tasks for each participant.

A set of instructions are also read before each of the separate conditions within the separate tasks.

Please refer to each of the separate motor task sections for 'participant instructions'.

Please read these instructions as accurately as possible to each participant.

Examiner bias can be reduced by ensuring that the instructions are read out clearly and precisely, as well as asking the participant if he/she has understood the instructions.

Please inform the participant that you will be reading out the instructions out loud.

Tell them that this is done to make sure that instructions are the same for everyone.

The general instructions are:

-The last tasks we will do today are a series of motor tasks. I am going to read the instructions out for you to insure that they are the same for every participant of this study.

-The tasks will be completed on the touch screen that you see here (point to the touch screen). You will see that the tasks are comparable to simple computer games you may have played before. If you have never played computer games before you do not need to worry- I will explain everything to you and you are given plenty of time to ask questions if you have them.

-Today I am asking you to complete 3 tasks.

This will take about 20 minutes.

These tasks will measure the how fast you can execute actions, how you plan your actions and how flexible you are in changing them.

-I will give you instructions before every task, to help you complete the task.

You will have time to ask questions before we start to ensure you have understood the instructions.

If you do not understand, please do not hesitate to ask me. It is very important that you understand exactly what you need to do.

-Some of these tasks measure reaction times. This means that you will have to react as fast as you can. However, please know that this is not a competition. You cannot do good or bad on these tasks.

-if you have any questions please ask them now.

Dutch:

-De laatste taken die we vandaag zullen gaan doen zijn een serie motorische taken.

- Alle instructies voor de taken zullen voorgelezen worden net als nu. Dit wordt gedaan omdat het belangrijk is dat de instructies voor iedereen gelijk zijn. Door de instructies voor te lezen zorgen wij hiervoor.

-De Motorische taken zullen met dit TouchScreen uitgevoerd worden (wijs touch screen aan)

-De taken zullen je waarschijnlijk herinneren aan computer spelletjes die je misschien eerder hebt gespeeld. Maak je geen zorgen als je nooit computer spelletjes speelt- ik zal alles zo duidelijk mogelijk uitleggen en je krijgt voldoende mogelijkheid om vragen te stellen.

-We zullen in totaal 4 taken uitvoeren wat ongeveer een uur zal duren

De taken zullen meten hoe secuur je een taken uitvoert- hoe snel je dit kunt- hoe je je acties gepland- en hoe flexibel je bent in het aanpassen als dit moet.

-Sommige taken zullen je reactie tijd meten. Dit betekent dat je zo snel als je kunt moet reageren. Dit betekent echter niet dat het een wedstrijdje is: Je kunt op deze taken niet goed of slecht presteren.

SPATIAL TAPPING TASK- Reaction and Movement Times

CODE 2

Spatial Tapping task general instructions

English

- The first task will measure your reaction time.
- There are 3 different levels in this task, which I will ask you to complete in 2 different ways.
- I will explain each of these levels and the different ways to complete them as we go through them.
- Do you have any questions? Let's get started.

Dutch

- De eerste taak meet je reactietijd.
- Er zijn 3 verschillende niveaus die op twee verschillende manieren uitgevoerd moeten worden.

CODE 2

Task 2 Conditions 1 instruction 1 trail 1

- We will start with part 1 instruction 1.
- When the task starts you will see a green square appear on a white screen.
- Please place your dominant hand's (can be left or right) index finger on the green square.
- Now, as soon as you hear the beep **ONE black dot** will appear on the screen.

-As fast as you can; lift your index finger *off* the green square *and onto* the black dot on the screen and back to the green square.

CODE 2

-Moving you index finger to the black dot as fast as you can is the most important of this task.

-Like this; (Illustrate the movement of 'square to dot')

- Do you have any questions? Let's get started

S...C1 I1 T1

Dutch

-We zullen nu beginnen met het eerste deel van de taak (deel 1 Instructie 1)

- Zodra de taak begint zul je een groen vierkant onder in het scherm zien. (linksonderin)

-Plaats hier de wijsvinger van je schrijfhand op.

-Op een gegeven moment zul je een toon horen en één stip op het scherm zien.

- Raak dan zo snel mogelijk de zwarte stip aan en ga weer terug naar het groene vierkant. Wacht daar tot de volgende stip verschijnt.

-Het is hier de bedoeling dat je zo snel mogelijk de stip aanraakt en terug naar het groene vierkant gaat en daar blijft.

-Zo (doe de beweging voor)

- Heb je nog vragen?

Task 1 Condition 2 instruction 1 trail 1

English:

- Now we will start with part 2 of instruction 1.
- Again please place your index finger on the green square on the white screen.
- Now as you hear the beep **TWO black dots** will appear on the screen.
- As fast as you can-lift your index finger **off** the green square **and onto** the black dots one after the other and from left to right and back to the green square.
- Moving you index finger to the black dots as fast as you can is the most important of this task.**
- Like this; (Illustrate the movement of 'square to dot')
- Do you have any questions? Let's get started

S...C2 I1 T1

Dutch

- We zullen nu beginnen met het tweede deel van de taak (deel 2 Instructie 1.)
- Zodra de taak begint zul je weer een groen vierkant onder in het scherm zien. (links onderin)
- Plaats daar weer je wijsvinger op
- Op een gegeven moment zul je een toon horen en TWEE stippen op het scherm zien.

- Raak dan zo snel mogelijk de stippen aan. Doe dit van links naar rechts en ga daarna weer terug naar het groene vierkant

-Het is hier de bedoeling dat je zo snel mogelijk de stippen aanraakt en terug naar het groene vierkant gaat en daar blijft. Dus houd daar je vinger totdat de volgende stip verschijnt.

-Zo (doe de beweging voor)

- Heb je nog vragen?

CODE 2

Task 1 Condition 3 instruction 1

English:

-Now we will start with part 3 instruction 1.

- Again please place your index finger on the green square on the white screen.

As soon as you hear the beep **THREE black dots** will appear on the screen.

-Now- as fast as you can- lift your index finger **off** the green square **and onto** the black dots in a sequence from left to right and back to the green square.

-**Moving you index finger to the black dot as fast as you can is the most important of this task.**

-Like this; (Illustrate the movement of 'square to dot')

- Do you have any questions? Let's get started

S...C3 I1 T1

Dutch

-We gaan nu beginnen met het derde deel van deze taak.

- *Plaats zometeen weer je wijsvinger op het groene vierkant onderin het scherm.*

Op een gegeven moment zul je een toon horen en DRIE stippen op het scherm zien.

- *Raak dan zo snel mogelijk de stippen aan.. Doe dit van links naar rechts en ga daarna weer terug naar het groene vierkant.*

-*Het is hier de bedoeling dat je zo snel mogelijk de stippen aanraakt en terug naar het groene vierkant gaat en daar blijft. Dus houd daar je vinger totdat de volgende stip verschijnt.*

-Zo (doe de beweging voor)

- Heb je nog vragen

CODE 2

Task 1 Condition 1 instruction 2

English:

-Now we will start part 1 of instruction 2.

- Again please place your index finger on the green square on the white screen.

-As soon as you hear the beep **ONE black dot** will appear on the screen.

- **The first movement is to lift your index finger as fast as you can. This is the most important movement here.**

- **Lift your finger as fast as possible from the green square in an abrupt movement.**

-**The second movement** is for you to move onto the black dots **in your own time**.

-Like this; (Illustrate the movement of 'square to dot')

S...C1 I2 T1

- Do you have any questions? Let's get started

Dutch

-We zullen nu beginnen met het vierde deel van deze taak. (deel 1 Instructie 2) Dit onderdeel zal iets anders zijn dan de vorige onderdelen.

- Plaats zometeen weer je wijsvinger op het groene vierkant onderin het scherm.

Op een gegeven moment zul je een toon horen en één stip op het scherm zien.

- Haal dan zo snel mogelijk je vinger van het groene vierkant en raak in je eigen tempo de zwarte stip aan. Ga daarna weer terug naar het groene vierkant.

-Het is dus de bedoeling dat je zo snel mogelijk het groene vierkant loslaat door je wijsvinger op te tillen.

-Je mag dan in je eigen tijd de stip aanraken en terug naar het groene vierkant gaan en daar blijven.

-Zo (doe de beweging voor)

- Heb je nog vragen?

CODE 2

Task 1 Condition 2 instruction 2

English:

- Now we will start with part 2 of instruction 2.
- Again please place your index finger on the green square on the white screen.
- As soon as you hear the beep **TWO black dots** will appear on the screen.
- The first movement is to lift your index finger as fast as you can. This is the most important movement here.**
- Lift your finger as fast as possible from the green square in an abrupt movement.**
- The second movement is for you to move onto the black dots in your own time in a sequence from left to right.**
- Like this; (Illustrate the movement of 'square to dot')
- Do you have any questions? Let's get started

S...C2 I2 T1

Dutch

-We zullen nu beginnen met het vijfde onderdeel van deze taak. Deze lijkt op het vorige onderdeel maar is nu met TWEE stippen.

-Plaats zometeen weer je wijsvinger op het groene vierkant onderin het scherm.

Op een gegeven moment zul je een toon horen en TWEE stippen op het scherm zien.

- Haal dan zo snel mogelijk je vinger van het groene vierkant en raak in je eigen tempo de zwarte stip aan. Ga daarna weer terug naar het groene vierkant.

-Het is dus de bedoeling dat je zo snel mogelijk het groene vierkant loslaat door je wijsvinger op te tillen.

-Je mag dan in je eigen tijd de stip aanraken en terug naar het groene vierkant gaan en daar blijven.

-Zo (doe de beweging voor)

- Heb je nog vragen?

CODE 2

Task 1 Condition 3 instruction 2

English:

-Now we will start with part 3 of instruction 2.

- Again please place your index finger on the green square on the white screen.

-As soon as you hear the beep **THREE black dots will appear on the screen.**

-The first movement is to lift your index finger as fast as you can. This is the most important movement here.

-Lift your finger as fast as possible from the green square in an abrupt movement.

-The second movement is for you to move onto the black dots in your own time in a sequence from left to right.

-Like this; (Illustrate the movement of 'square to dot')

- Do you have any questions? Let's get started

S...C3 I2 T1

Dutch

-We zullen nu beginnen met het laatste deel van de taak.

-Plaats zometeen weer je wijsvinger op het groene vierkant onderin het scherm.

-Op een gegeven moment zul je een toon horen en DRIE stippen op het scherm zien.

- Haal dan zo snel mogelijk je vinger van het groene vierkant en raak in je eigen tempo de zwarte stip aan. Ga daarna weer terug naar het groene vierkant.

-Het is dus de bedoeling dat je zo snel mogelijk het groene vierkant loslaat door je wijsvinger op te tillen.

-Je mag dan in je eigen tijd de stip aanraken en terug naar het groene vierkant gaan en daar blijven.

-Zo (doe de beweging voor)

- Heb je nog vragen?

TASK 2- Flexibility/Stability

CODE 3

Task 2 General instructions

English:

-This next task measures your planning abilities.

-This task is made up out of 3 parts.

-I will guide you through each of these parts as we go along.

-Shortly you will see a circle of dots on the screen.

- Do you have any questions? Let's get started

Dutch:

We zullen nu beginnen met de tweede taak. Deze meet je planningsvermogen en bestaat uit drie delen

Het vaste onderdeel van deze taak is een cirkel van stippen op het scherm

Task 2 Condition 1

-Now we will start with part 1

-A circle of dots will appear on the screen in front of you

-As soon as the dots appear please touch each of the dots with your index finger in an anti-clockwise fashion **starting with** the bottom right dot on the screen.

-Please go around the circle touching these dots **at a rhythm that is comfortable for you.**

-Like this; (Illustrate the movement)

-The task will end when the screen goes blank

-Before we start we will begin with a practice run (Use code SxC1R0T1)

-We will now do the same again (Use code SxC1R0T2).

-This later attempt will be the actual measured part of this task

-Do you have any questions? Let's get started

Dutch:

-We zullen nu beginnen met het eerste deel van deze taak

-Zodra je de cirkel met stippen op het scherm ziet, is het de bedoeling dat je deze individueel aanraakt en het cirkeltje tegen de klok in rondgaat

-Begin op de stip rechts onder in het scherm

S...C1 R0 T1

-Blijf dit doen tot het scherm verdwijnt.

-We zullen eerst een oefenronde inlassen zodat alles duidelijk is voor je (gebruik code SxC1R0T1). Hierna volgt de ronde die uiteindelijk meetelt in het onderzoek.

- Heb je nog vragen?

S...C1 R0 T2

-Dit zullen we nu nogmaals doen (gebruik code SxC1R0T2)

-Deze laatste ronde wordt gemeten en is de ronde die uiteindelijk meetelt in het onderzoek

-Heb je nog vragen?

NOTEER SPONTANE RITME 'ALL TAPS'.

CODE 3

Task 2 Condition 2

- Now we will start with the second part of this test
- Again, a circle of dots will appear on the screen in front of you, just like before
- You will now hear a **tone** to which you must match the touching of the dots in an anti-clockwise fashion.
- Please **start at** the bottom right dot on the screen.
- Please touch each of the dots with your index finger at the exact time you hear the tone.
- Please try to synchronise **your touch with the tone**
- Again we will first start with a practice round
- (Use for practice R1100 and T1).(Then use T2 for actual trails)
- Each trail will have a slightly different rhythm of the tones which you need to adjust to
- The task will end when the screen goes blank
- Do you have any questions? Let's get started

Dutch:

- We beginnen nu met het tweede deel van de taak**

- We zullen weer eerst een oefenronde inlassen zodat alles duidelijk is voor je** (gebruik voor oefenronde R1100 en T1. Gebruik daarna T2 voor alle metingen)

- **Zodra je weer de cirkel met stippen ziet, zul je ook een toon horen.**

- Het is het de bedoeling dat je de stippen weer individueel aanraakt en het cirkeltje tegen de klok in rondgaat**

-Maar dit keer precies op het ritme van de toon. (dus neerkomen op het moment van de toon)

-Begin weer bij de stip rechts onder in het scherm

-Dit moet je blijven doen totdat het scherm verdwijnt.

-Hierna zullen we dit nog 9 keer doen, elke keer zal de toon een ander ritme aangeven.

-Alleen deze laatste 9 ronden worden gemeten en zijn de rondes die uiteindelijk meetellen in het onderzoek

-Heb je nog vragen?

S...C2 R1100 T1 (oefenronde)	S...C2 R1100 T2	S...C2 R400 T2
	S...C2 R700 T2	S...C2 R300 T2
	S...C2 R500 T2	

CODE 3

Task 2 Condition 3

-Now we will start with the third part of this test

-Again, a circle of dots will appear on the screen in front of you

-Again, you will now hear a **tone** to which you must match the touching of the dots in an anti-clockwise fashion

-Again, please **start at** the bottom right dot on the screen.

-Again, please touch each of the dots with your index finger at the exact time you hear the tone.

AND try to synchronise **your touch with the tone**

-This time, you will see **flashing and moving dots**.

-Please try to **not to get distracted** by these flashing dots and keep both your rhythm and touch synchronised.

-Do you have any questions? Let's get started

Dutch:

-We beginnen nu met het laatste deel van deze taak

-Deze keer zullen we geen oefenronde inlassen, want je weet inmiddels hoe de taak uitgevoerd moet worden.

-Net als hiervoor zal er een cirkel met stippen op het scherm verschijnen.

-Zodra je de cirkels ziet zul je ook weer de toon horen

-Het is het de bedoeling dat je de stippen weer individueel aanraakt en het cirkeltje tegen de klok in rondgaat op het ritme van de toon.

-Begin weer op de stip rechts onder in het scherm

-Maar deze keer zul je ook andere stippen zien oplichten of stippen op het scherm zien verschijnen die je proberen af te leiden.

-Probeer je NIET af te laten leiden en voltooi de taak zoals je hiervoor ook hebt gedaan

-Blijf dit doen tot het scherm verdwijnt.

-Er zijn in totaal 3 rondes; elke ronde zal je op een andere manier proberen af te leiden.

-Heb je nog vragen?

[Vul het spontane ritme in]

S...C3 R..... T1

S...C5 R..... T1

TASK3 SELECTIVE REACTION TIME

Task 3 general instructions (NO YES/NO OPTION)

CODE 5

English:

-This next task consists of two parts.

-I will explain as we go along.

- In both conditions you will be asked to keep your index finger on the green square- just like in the last task.

-Then letters or numbers will appear in the middle of the screen which you will need to touch and then go back to the green dot where you will wait for the next symbol to appear.

-We will now start with the first part of the task

- Do you have any questions? Let's get started

Dutch:

-We gaan nu beginnen met de laatste taak van vandaag

De taak bestaat uit 2 onderdelen.

Bij beide onderdelen plaats je je wijsvinger op het groene vierkant (links onderin; wijs aan)

Iets daarboven (plek aanwijzen) **zullen letters of cijfers verschijnen.**

Raak deze dan aan, en ga weer terug naar het groene vierkant. Wacht daar tot het volgende symbool zal verschijnen.

Heb je hierover vragen?

CODE 5

Task 3 Condition 1 (NO YES/NO OPTION)

English:

-We will now start the first part of the task

-Please rest your index finger on the green dot- which will appear here (point to area)

-Shortly you will see a either a letter or a number dot on the screen.

-Please touch the dot with your index finger and then go back to touching the green square where you wait for the next symbol to appear.

-The most important part of this task is to move to the symbol as fast as you can and then back to the green square.

- Do you have any questions? Let's get started

S... C1

Dutch:

-Dan zullen we nu starten met het eerste deel van de taak.

Plaats dus je wijsvinger op het groene vierkant links onderin het scherm.

Raak de letters en cijfers aan die op het scherm verschijnen zo snel mogelijk aan, en ga weer terug naar het groene vierkant. Daar wacht je tot het volgende symbool weer verschijnt.

-Heb je nog vragen? Dan gaan we nu beginnen.

CODE 5

Task 3 Condition 2 (NO YES/NO OPTION)

English:

- Now we are ready to start the second part of this task.

-Shortly you will see a symbol, which can be number or a letter, on the screen.

-Please **only** touch the symbol if you see a **letter**. **Then move back** to the green square on the bottom of the screen.

-Remember that it is counted as a mistake if you move off the green square if it is not a letter.

- Do you have any questions? Let's get started

S... C2

Dutch:

-Dan zullen we nu starten met het tweede deel van deze taak.

-Laat je wijsvinger weer rusten op het groene vierkant.

Je zal kort een symbool op het scherm zien

-Deze symbolen kunnen letters of cijfers zijn.

-Raak alleen het symbool aan als dat een letter is en ga weer terug naar het groene vierkant

-Negeer de cijfers; blijf dan gewoon op het groene vierkant

-Heb je nog vragen? Dan gaan we nu beginnen.

THE END

CODE 6