Cognitive Flexibility in Neurological Disorders: Cognitive Components and Event-related Potentials

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Abstract

Performance deficits on the Wisconsin Card Sorting Test (WCST) in patients with prefrontal cortex (PFC) lesions are traditionally interpreted as evidence for a role of the PFC in cognitive flexibility. However, WCST deficits do not occur exclusively after PFC lesions, but also in various neurological and psychiatric disorders. We propose a multi-component approach that can accommodate this pattern of omnipresent WCST deficits: the WCST is not a pure test of cognitive flexibility, but relies on the effective functioning of multiple dissociable cognitive components. Our review of recent efforts to decompose WCST performance deficits supports this view by revealing that WCST deficits in different neurological disorders can be attributed to alterations in different components. Frontoparietal changes underlying impaired set shifting seem to give rise to WCST deficits in patients with amyotrophic lateral sclerosis, whereas the WCST deficits associated with primary dystonia and Parkinson's disease are rather related to frontostriatal changes underlying deficient rule inference. Clinical implications of these findings and of a multi-component view of WCST performance are discussed.

Keywords: cognitive flexibility; Wisconsin Card Sorting Test (WCST); set shifting; rule inference; Parkinson's disease; primary dystonia; amyotrophic lateral sclerosis; event-related potentials.

1. Cognitive Flexibility and the Wisconsin Card Sorting Test

Cognitive flexibility can be broadly defined as the ability to switch perspectives, thoughts, thinking styles, and strategies (Diamond, 2013). More frequently, however, cognitive flexibility is treated synonymously with the more specific term *cognitive set shifting* (Ionescu, 2012; Johnco, Wuthrich, & Rapee, 2014; Miyake et al., 2000). A cognitive set involves the representations and processes that are necessary to perform a particular task (Schneider & Logan, 2014). Being able to shift between cognitive sets allows multitasking and adapting to changing environmental demands.

The construct of cognitive flexibility has received attention from numerous subfields of psychology and the neurosciences (Altamirano, Miyake, & Whitmer, 2010; Dias, Robbins, & Roberts, 1997; Hazy, Frank, & O'Reilly, 2007; Logue & Gould, 2016; Vandierendonck, Liefooghe, & Verbruggen, 2010; Zelazo, 2006). This multidisciplinary interest in cognitive flexibility has stimulated the development of various assessment tools including questionnaire measures (Dennis & Vander Wal, 2010; Martin & Rubin, 1995) and variants of the experimental task-switching paradigm (Kiesel et al., 2010). In neuropsychology, standardized tests such as the Wisconsin Card Sorting Test (WCST, Berg, 1948; Grant & Berg, 1948; Heaton et al., 1993), the intra-dimensional/extra-dimensional set-shift task of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Downes et al., 1989) or the Trail-Making Test (TMT, Reitan, 1992) are widely used to investigate the relationship between neurological diseases and decrements in cognitive flexibility.

The WCST is perhaps the most frequently used neuropsychological test for the assessment of cognitive flexibility (Rabin, Barr, & Burton, 2005). On the WCST, examinees have to sort cards in accordance with one of three viable task rules (color, shape, number). In order to identify the currently prevailing task rule, they have to rely on the examiner's feedback. Positive feedback after correct card sorts indicates that the applied task rule should be repeated

on the next trial. Negative feedback after applying a previously correct rule indicates that the valid task rule has changed. When being informed about a shift in task rules, examinees are required to test hypotheses concerning the new rule. Having identified the correct new rule, examinees have to maintain it until they are informed that the rule has changed again. The valid rule (or category) changes after a defined number of consecutive correct responses. Although numerous WCST performance scores have been proposed (Heaton et al., 1993), neuropsychologists often focus on the number of completed categories and the number of perseverative errors (i.e., repeated applications of the same incorrect rule) as dependent variables (Nyhus & Barceló, 2009). An exemplary trial sequence on the WCST is shown in Figure 1.

(please insert Figure 1 about here)

2. The Omnipresence of WCST Performance Deficits

In one of the most seminal papers in the field of clinical neuropsychology, Milner (1963) examined the impact of unilateral cortical excisions on WCST performance in patients who underwent neurosurgical treatment for the relief of focal epilepsy. In contrast to patients with posterior cortical lesions, patients with lesions in the dorsolateral prefrontal cortex (PFC) completed fewer categories and committed more perseverative errors on the WCST. This pattern of results has been replicated several times (Nyhus & Barceló, 2009) and two meta-analyses confirmed the WCST's sensitivity to frontal lobe damage (Alvarez & Emory, 2006; Demakis, 2003). Findings along these lines have contributed to the widespread consensus that structures of the PFC underlie executive functioning in general and cognitive flexibility in particular (Miller & Cohen, 2001).

However, while the sensitivity of the WCST to PFC lesions is largely uncontested, WCST performance deficits are not limited to patients with PFC damage. Challenging their specificity to PFC dysfunctions, WCST deficits have also been found in a variety of

neurological and psychiatric disorders, including Parkinson's disease (PD; Dirnberger & Jahanshahi, 2013; Kudlicka, Clare, & Hindle, 2011), amyotrophic lateral sclerosis (ALS; Beeldman et al., 2016; Lange, Vogts et al., 2016), primary dystonia (Lange, Seer, Salchow et al., 2016), Gilles de la Tourette syndrome (Lange, Seer, Müller-Vahl, & Kopp, 2017), eating disorders (Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007), attention deficit hyperactivity disorder (Romine et al., 2004), depression (Snyder, 2013), and obsessive-compulsive disorder (Shin, Lee, Kim, & Kwon, 2014). It is noteworthy that despite the substantial differences between these clinical conditions, WCST performance deficits are remarkably similar in size (typically around $d = 0.5$) in the meta-analyses cited above.

Most attempts to account for this pattern of unspecific WCST performance deficits are rather unsatisfactory from a neuropsychological perspective. One possibility would be to assume that all the listed disorders involve a common deficit of similar severity in a brain area (e.g., the PFC; Milner, 1963) or a neural network (e.g., frontostriatal circuits; Hazy et al., 2007) that is critical for cognitive flexibility as measured by the WCST. This explanation is rendered rather implausible by the heterogeneity among these disorders. Alternatively, it could be argued that WCST performance relies on a brain network that is much less clearly circumscribed than commonly assumed. However, given the variety of the affected patient groups, this network would need to be so large and widespread that the scientific value of such an explanation would be marginal. A third possible explanation attributes the group differences found in neuropsychological studies comparing patients with a specific disease and healthy control participants to disease-unspecific factors. Independent of their particular disorder, patients might be distracted by their symptoms during neuropsychological testing (Jahanshahi et al., 2014; Jahanshahi et al., 2003) or perform worse because of the expectation of being cognitively impaired (Schwarz, Pfister, & Büchel, 2016). If such unspecific factors underlie the omnipresence of WCST performance deficits in clinical conditions, WCST findings would not be very informative with regard to the neural underpinnings of cognitive flexibility.

Here, we propose a different possibility to account for similar WCST deficits in highly diverse clinical conditions. We submit that multiple processes (both on the cognitive and on the neural level) interact in giving rise to WCST performance. We will refer to these processes as "WCST components" in the following. WCST performance deficits can result from dysfunction in any one of these components. This implies that phenotypically similar WCST deficits in different patient groups might, in fact, arise from impairment in different (cognitive or neural) processes. For example, a particular WCST component might be affected by the neurodegenerative changes occurring in the context of PD, but the same component may remain intact in patients with affective disorders, whose WCST deficits are best explained by dysfunction in a different component. In the following, we will briefly review the evidence for this multi-component structure of the WCST, thereby focusing on previous attempts to dissociate different cognitive components underlying WCST performance.

3. Dissociating the Multiple Components of WCST Performance

It has been argued before that the WCST cannot be regarded as a pure test of cognitive flexibility (Miyake & Friedman, 2012; Strauss, Sherman, & Spreen, 2006). Closer inspection of its task structure reveals that the WCST requests multiple additional cognitive processes including category formation, set maintenance, working memory, and rule inference (Buchsbaum et al., 2005; Dehaene & Changeux, 1991; Ridderinkhof, Span, & van der Molen, 2002). This implies that WCST performance deficits in a particular clinical population cannot unequivocally be attributed to cognitive inflexibility (Cools, Barker, Sahakian, & Robbins, 2001). When a patient commits a perseverative error on the WCST, it is possible that this patient indeed lacks the cognitive flexibility required to abandon the previously applied rule. However, perseverative errors might also arise from an inability to realize that the WCST cards can be sorted according to different task rules. Similarly, even a highly flexible individual who can respond to all three WCST rules may commit a large number of perseverative errors (just by

chance alone) when not being able to remember the previously applied task rule. Disentangling the different components that contribute to observed WCST performance deficits may thus help to account for the omnipresence of WCST deficits in clinically diverse conditions. In addition, clinical decision-making based on WCST results requires detailed information about the components contributing to WCST performance deficits in a particular patient. For example, patients with a specific deficit in cognitive flexibility are unlikely to benefit from mnemonic devices, whereas the same technique might be very effective in patients who perform poorly on the WCST because of (working) memory impairment (Hartman, Bolton, & Fehnel, 2001).

A number of methodological approaches have been proposed to account for the multi-component structure of the WCST. In the following, we will review five different strategies that share the common goal of decomposing the complex cognitive and neural processes that give rise to performance on the WCST.

3.1 Designing Pure Tasks

One possible way to decompose WCST performance is to develop new paradigms that focus on a subset of the processes required by the WCST. For example, the intra-dimensional/extra-dimensional set-shift task has been proposed to measure different WCST component processes at distinct stages of the task (Downes et al., 1989). Moreover, research in the field of experimental psychology has led to the development of numerous variants of the task-switching paradigm (Kiesel et al., 2010). In contrast to the WCST, most task-switching paradigms are likely to provide relatively pure estimates of cognitive flexibility due to substantially reduced demands on working memory, category learning, and rule inference (Buchsbaum et al., 2005). While innovation with regard to paradigm design is certainly desirable, one problem associated with this approach is the largely unknown relation between novel paradigms and the WCST. Correlations between task-switching performance and the number of perseverative errors on the WCST are typically low (Miyake et al., 2000). As a

consequence, the implications of disturbed task-switching performance in neurological (Das & Wylie, 2014) and psychiatric disorders (Ravizza & Salo, 2014) for the understanding of WCST performance deficits in these patients remain elusive. Extensive research focusing on the commonalities between the WCST and task-switching paradigms (Buchsbaum, 2005; Gamboz, Borella, & Brandimonte, 2009; Miyake et al., 2000) is still required before task-switching findings can inform the interpretation of clinical WCST data.

3.2 Manipulating Demands on Isolated Cognitive Functions

An alternative approach is illustrated by the studies of Hartman and colleagues (Hartman et al., 2001; Hartman, Steketee, Silva, Lanning, & Andersson, 2003) who asked their participants to complete multiple variants of the WCST while systematically manipulating the demands for a particular cognitive process (in their case, working memory). Using this method, they showed, for example, that the consistently reported age-related decline in WCST performance (Rhodes, 2004) almost disappeared when external memory cues were provided (Hartman et al., 2001). In a similar study, patients with inferior medial frontal cortex lesions were observed to be relatively unaffected in their performance on a traditional version of the WCST. However, these patients showed marked performance decrements when being explicitly informed what the three possible task rules were, possibly because these instructions triggered additional executive processes that interfered with automatic processing (Stuss et al., 2000). While this approach may provide valuable insights into the precise processes underlying WCST performance deficits in groups of patients, its potential for translation into clinical practice seems limited. Administering multiple variants of the WCST would consume a large amount of resources both on the part of the clinician and on the part of the patient. Hence, in the context of clinical neuropsychological assessment, it seems hardly feasible to assess individual patients' performance across multiple conditions of sophisticated WCST experiments.

3.3 Identifying Latent Dimensions

Factor analytical studies build on data from a standard version of the WCST and aim to identify latent dimensions that explain the variance common to different WCST scores (Greve, Ingram, & Bianchini, 1998; Greve et al., 2002). While these studies consistently identify a "general executive functioning" factor (Greve, Stickle, Love, Bianchini, & Standford, 2005, p. 362), which can be measured with reasonable precision, it still remains unclear which cognitive processes are reflected by this factor. Problem-solving and set-maintenance processes have been proposed to contribute additional variance, but it appears that these processes cannot be accurately measured by factors relying on the standard scores of the WCST (Greve et al., 2005).

3.4 Dissociating Patterns of Erroneous Responses

These results from factor analytical studies suggest that the performance scores offered by standard versions of the WCST (Grant & Berg, 1948; Heaton et al., 1993; Nelson, 1976) might not be sufficient to assess the distinct cognitive processes that are required for performing the WCST. Although the number of perseverative errors might be the most popular WCST index (Godinez et al., 2012) and the measure most affected by cortical lesions (Greve et al., 2005), a more detailed analysis of different error types may prove valuable in distinguishing the cognitive components of WCST performance (Barceló, 1999; Godinez et al., 2012). Previous studies adopting this approach mostly focused on the comparison between perseverative and non-perseverative errors (with the latter category comprising all errors that do not meet the criteria for a perseverative error; Demakis, 2003; Li, 2004; Milner, 1963). However, extensive work by Barceló and colleagues has shown that the analysis of non-perseverative errors along traditional lines confounds what they called "efficient errors" and "inefficient errors" (Barceló, 1999; Barceló & Knight, 2002; Barceló, Muñoz-Céspedes, Pozo, & Rubia, 2000; Nyhus & Barceló, 2009).

Efficient errors occur in the context of an efficient trial-and-error process following a shift in task rules. Being informed that the previously applied rule is no longer valid, examinees have to choose one of the two remaining task rules on the next trial. Even an ideally performing individual can be expected to commit efficient errors on fifty percent of the shift trials because he or she can only guess which one of the two possible rules is correct (Kopp & Lange, 2013). The number of efficient errors is typically negatively correlated with all other WCST error measures, indicating that efficient errors are not indicative of a WCST performance deficit (Godinez et al., 2012). It is thus not surprising that combining efficient and inefficient non-perseverative errors into a single measure obscured a clear group difference between patients with PFC lesions and healthy controls in the study by Barceló and Knight (2002). As a result of these studies, inefficient non-perseverative errors (also referred to as distraction errors) have been proposed to provide a comparatively clean measure of set-maintenance processes on the WCST (Barceló, 1999; Nyhus & Barceló, 2009).

In a recent study using a computerized version of the WCST (cWCST), we have shown that inefficient non-perseverative errors can and should be further subdivided as they can result from deficits in at least two distinct components of the WCST: set maintenance and rule inference (Lange, Kröger et al., 2016). According to this view, impairments in these processes are reflected in two different error measures: the number of set-loss errors and the number of integration errors (see Figure 2). An individual commits a set-loss error when not maintaining the sorting rule although the experimenter's feedback has indicated that this rule is correct. An integration error, on the other hand, is scored when—after a change in task rules—the individual fails to infer the correct new task rule although all necessary information has been given.

Our analyses revealed that the majority of inefficient non-perseverative errors do not arise from failures to maintain set but rather from deficits in rule inference. In comparison to most other tasks that have been proposed to assess cognitive flexibility (Kiesel et al., 2010),

temporary uncertainty about the correct rule is a unique characteristic of the WCST (Kopp & Lange, 2013). After being cued to shift rules, examinees do not know which of the two remaining rules might be correct. They have to arbitrarily decide for one rule and only after testing this rule, they have the information necessary to determine which of the rules is correct. However, healthy participants in an age diverse sample (M_{age} = 50 yrs, SD_{age} = 17 yrs) failed to integrate this information and to infer the correct rule on almost 30 % of the respective trials. This type of error (i.e., the integration error) was considerably more frequent than perseverative errors (11 %) or set-loss errors (4 %).

Our study further demonstrated that perseverative errors, set-loss errors, and integration errors on the cWCST can be dissociated as indicators of distinct WCST components (i.e., set shifting, set maintenance, and rule inference, respectively). More specifically, it was only the number of integration errors that increased significantly with participants' age, indicating that age-related changes in WCST performance (see Rhodes, 2004) are due to deficits in rule inference rather than in cognitive set shifting or set maintenance. This age-related decline in rule-inference efficiency may be linked to reduced working memory capacity in older individuals (Hartman et al., 2001). The relevance of working memory capacity for rule inference on the WCST was further corroborated by data from an experimental study in young individuals (Lange, Kröger et al., 2016). In this study, we manipulated the number of viable WCST rules (three vs. four) by adding a fourth stimulus dimension (i.e., shading), which constituted a possible sorting rule in four-rule conditions but not in three-rule conditions. Our results revealed that only the number of integration errors increased with the number of cWCST rules, indicating that rule inference becomes more difficult when information about more rules has to be stored and integrated in working memory. In combination, these results indicate that by extending the range of traditional WCST scores to include integration errors, it is possible to assess a previously neglected yet important facet of WCST performance. They also illustrate

how a detailed analysis of erroneous responses on the cWCST can inform our understanding of WCST deficits in a particular population (in this case, healthy elderly participants), thus highlighting the potential of this approach to identify the components that give rise to WCST deficits in various clinical conditions (see Teubner-Rhodes, Vaden Jr., Dubno, & Eckert, 2017, for a related approach).

(please insert Figure 2 about here)

3.5 Dissociating Patterns of Neural Responses

The components of WCST performance cannot only be distinguished on the behavioral level but also with regard to the neural responses to different events within the WCST. Using fMRI, Monchi and colleagues (2001) investigated the patterns of neural activity related to the rule transition phase of an fMRI-compatible version of the WCST (see Alvarez & Emory, 2006, for an overview of imaging studies using similar approaches). They found increased activity in the executive frontostriatal circuit (including the PFC and the caudate nucleus) in response to the presentation of shift cues (i.e., feedback stimuli signaling that the rule has to be shifted). In contrast, when participants were required to apply the new rule (i.e., when they had to match cards after having received a shift cue), the motor frontostriatal circuit (including the premotor cortex and the putamen) was observed to be more active. While such results provide valuable insights into the neural substrates of WCST performance, the conclusions drawn from imaging studies are limited by the poor temporal resolution of fMRI.

The successful shift from one rule to another likely requires a number of different cognitive processes that occur in quick succession after an individual encounters a signal to shift rules. For example, individuals first need to allocate the necessary attentional resources to the shift signal to infer the currently valid rule and then to use the extracted information to change cognitive set. These processes have been associated with distinct deflections in the

event-related potential (ERP; Barceló, Periáñez, & Knight, 2002; Cunillera et al., 2012; Kopp & Lange, 2013).

ERPs represent event-synchronized neural activities that can be obtained from the scalp-recorded electroencephalogram (EEG; Luck, 2014). They are thought to reflect the summation of postsynaptic potentials of large ensembles of synchronously active pyramidal neurons in the cerebral cortex (Woodman, 2010). The voltage deflections comprising the ERP have been related to distinct stages of information processing (Duncan et al., 2009). Due to its excellent temporal resolution, the ERP technique allows measuring these processing activities on the order of milliseconds (Altenmüller, Gerloff, & Münte, 2005; Picton et al., 2000). By recording the EEG while participants complete the cWCST, it is possible to assess and disentangle neural correlates of the cognitive processes underlying WCST performance (Barceló, 2003; Barceló, 1999; Barceló, et al., 2000; Barceló, Sanz, Molina, & Rubia, 1997; Kopp & Lange, 2013; Mattes, Cohen, Berg, Canavan, & Hopmann, 1991; Vilà-Balló et al., 2015). Note that this approach relies on the assumption that the cWCST requires cognitive processes that are similar to those required by standard versions of the WCST. Studies using the cWCST consistently detected two ERP deflections that appear to relate to dissociable cognitive components of WCST performance: the P3a and the posterior switch positivity (PSP; Figure 3).

The P3a is a positive ERP deflection with frontocentral scalp distribution whose generation likely involves prefrontal cortical areas (Polich, 2007; Volpe et al., 2007; Wronka et al., 2012) and possibly the striatum (Solís-Vivanco et al., 2015). Its amplitude has been linked to the efficiency of attentional orienting (Daffner et al., 1998, Hölig & Berti, 2010, Kopp, Tabeling, Moschner, & Wessel, 2006). When recorded in the cWCST, the P3a typically peaks between 300 and 500 ms after stimulus onset. In this paradigm, prominent P3a deflections have been observed in response to shift cues (Barceló et al., 2002; Barceló, Escera, Corral, & Periáñez, 2006; Cunillera et al., 2012). However, the amplitude of the P3a also appears to be

enhanced following first repeat cues (i.e., feedback stimuli signaling that the correct rule has been identified and can now be maintained) when compared to repeat cues that occur later in a series of rule repetitions (Cunillera et al., 2012; Kopp & Lange, 2013). First repeat cues are particularly informative as they eliminate participants' uncertainty about the currently prevailing rule. Based on these results, the P3a has been proposed to reflect the proactive orienting of attentional resources to those stimuli that eliminate rule uncertainty and thus allow inferring the correct WCST rule (Kopp & Lange, 2013; Lange, Seer, Finke, Dengler, & Kopp, 2015). Preliminary evidence for a correlation between P3a amplitudes and the number of integration errors on the cWCST further supports the link between the P3a and the rule-inference component of the WCST (Lange, Seer, Finke et al., 2015).

In addition, a more posteriorly distributed positivity has been observed in ERP studies using the cWCST (Barceló, 2003; Kopp & Lange, 2013) or variants of the task-switching paradigm (Karayanidis et al., 2010). In contrast to the P3a, this positivity reaches its maximum at a later point in time (usually between 500 and 1000 ms after stimulus onset). Shift cues typically elicit larger and/or more sustained positivities than repeat cues (Gajewski & Falkenstein, 2011; Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2011; Karayanidis et al., 2010; Karayanidis & Jamadar, 2014; Kopp, Lange, Howe, & Wessel, 2014; Tarantino, Mazzonetto, & Vallesi, 2016). The term *PSP* refers to the difference potential that is obtained by contrasting the ERP deflections elicited by shift cues and repeat cues (Figure 3). The PSP likely results from the activation of frontoparietal brain networks (Karayanidis et al., 2010). There is widespread consensus that the PSP reflects neural activity for the shifting of cognitive sets (i.e., for cognitive flexibility in the narrower sense; Elchlepp, Lavric, Chambers, & Verbruggen, 2016; Jamadar, Hughes, Fulham, Michie, & Karayanidis, 2010; Karayanidis et al., 2010; Lange, Seer, Müller, & Kopp, 2015; Lavric, Mizon, & Monsell, 2008).

(please insert Figure 3 about here)

Against this background, we propose that the comparative analysis of P3a and PSP deflections elicited by cues on the cWCST allows dissociating the neural mechanisms underlying rule inference and set shifting and thus decomposing WCST performance. Similar to the more detailed analysis of different types of errors, the analysis of ERPs might contribute to a more accurate assessment of the components giving rise to successful performance on the WCST and its computerized analogue. Resolving the complexity of the WCST by analyzing multiple performance measures and ERP deflections (Figure 4) bears the potential to identify the sources of observed WCST deficits in particular clinical populations.

(please insert Figure 4 about here)

4. WCST Component Deficits in Neurological Disorders

In the remainder of this article, we demonstrate how the analysis of dissociable behavioral and neural response patterns on the cWCST can be used to identify the components that give rise to phenotypically similar WCST performance deficits in diverse clinical conditions. In our clinical studies of WCST deficits, we focused on neurological disorders that primarily affect motor functioning, including PD, ALS, and primary dystonia. Table 1 displays an overview of these disorders. Meta-analyses have shown that all three conditions are associated with medium-sized performance deficits on standard versions of the WCST (Beeldman et al., 2016; Kudlicka et al., 2011; Lange, Seer, Salchow et al., 2016; Lange, Vogts et al., 2016). Hence, WCST findings in these selected disorders can be regarded as quite representative for the broader WCST literature, where differences between healthy controls and non-demented patients with various disorders are typically in the order of half a standard deviation (see Section 2). By contrasting the results of our detailed analysis of cWCST error types and ERP correlates across patient populations, we examine whether similar overt WCST deficits can be attributed to deficits in similar vs. different WCST components.

(please insert Table 1 about here)

4.1 Parkinson's Disease

In PD, degeneration of dopaminergic neurons in the substantia nigra pars compacta leads to dopamine depletion in the dorsal striatum which, in turn, gives rise to motor symptoms such as bradykinesia, rigidity, and tremor (Kish, Shannak, & Hornykiewicz, 1988; Kordower et al., 2013; Rodriguez-Oroz et al., 2009). This lack of dopamine in the dorsal striatum and dysfunction in the associated frontostriatal loops has been proposed to also underlie patients' cognitive deficits on tasks like the WCST (Cools, Barker, Sahakian, & Robbins, 2003; MacDonald & Monchi, 2011; Robbins & Cools, 2014; Monchi, Hanganu, & Bellec, 2016).

In a study involving 32 patients with PD and 35 healthy matched control participants, we combined the use of the cWCST with the recording of ERPs to characterize the components underlying PD-related WCST deficits (Lange, Seer, Loens et al., 2016). In line with studies using standard versions of the WCST (Gotham et al., 1988) or other computerized WCST variants (Monchi et al., 2004), PD patients in our study committed more perseverative errors and more set-loss errors than healthy controls. This behavioral deficit was accompanied by substantially attenuated P3a amplitudes. As P3a amplitude attenuation in PD was not specific (i.e., restricted to informative first repeat feedback stimuli) and the number of integration errors was not significantly increased in patients with PD, PD-related changes in cWCST performance do not seem to be primarily related to deficient rule inference. Instead, non-selectively attenuated P3a amplitudes in patients with PD might be indicative of a general deficit in attentional orienting. Supporting the relevance of this attentional deficit for cWCST performance, regression analysis revealed that P3a amplitudes and amplitudes in the PSP analysis window interactively contributed to the prediction of the number of perseverative errors committed by patients with PD.

4.2 Amyotrophic Lateral Sclerosis

In ALS, neurodegeneration has traditionally been thought to be restricted to motor pathways. Over the last 20 years, it became increasingly recognized that ALS also extends to prefrontal cortical areas (Tsermentseli, Leigh, & Goldstein, 2012) and also affects frontoparietal cortical networks (Tedeschi et al., 2012), which seem to be critical for WCST performance (Agosta et al., 2013; Alvarez & Emory, 2006).

In contrast to PD, our studies involving patients with ALS revealed a substantial alteration in the specific neural correlates of set-shifting processes. In a first study, we investigated cWCST performance measures and ERP amplitudes in 21 patients with ALS and 21 matched controls (Lange, Vogts et al., 2016). In addition to increased perseverative errors and integration errors, we also found significantly attenuated PSP amplitudes in patients with ALS. A follow-up study using an independent patient sample of similar size (26 patients, 28 controls) suggests that the ALS-related attenuation of PSP amplitudes is not bound to a particular paradigm (Lange, Lange et al., 2016). In this study, we applied a relatively pure set-shifting task associated with substantially reduced demands on other cognitive processes (e.g., working memory, category learning, rule inference; see also Kopp et al., 2006, 2014). In line with our previous study, set-shifting specific ERP activity (i.e., the amplitude of the PSP) was substantially reduced in patients with ALS. Of note, attenuated PSP amplitudes were also observed in ALS patients who did not show any signs of cognitive impairment in neuropsychological assessment. Hence, attenuated PSP amplitudes in ALS may reflect subtle changes in cognitive set shifting before these changes can be detected on the behavioral level.

4.3 Primary Dystonia

In contrast to PD and ALS, primary dystonia develops in the absence of overt neurodegeneration (Breakefield et al., 2008). However, neuroimaging data indicate that primary dystonia is related to microstructural and functional brain alterations, predominantly in the basal ganglia and their cortical projection sites (Zoons, Booij, Nederveen, Dijk, & Tijssen,

2011). These neural changes might account not only for motor symptoms but also for the cognitive deficits associated with primary dystonia (Bugalho et al., 2008).

For our studies on WCST deficits in primary dystonia, we focused on patients with blepharospasm, a form of primary dystonia characterized by cramps of the muscles around the eyes (Tarsy & Simon, 2006). In contrast to a sample of 34 healthy controls, we found the number of integration errors to be selectively increased in a sample of 18 patients with blepharospasm (Lange, Seer, Salchow et al., 2016). An additional analysis (Lange, Seer, Dengler, Dressler, & Kopp, 2016) suggests that the increased number of integration errors in patients with blepharospasm is unlikely to result from the potentially distracting influence of motor symptoms in these patients (cf. Jahanshahi et al., 2003; 2014). In this study, cWCST performance was compared between blepharospasm patients and patients with hemifacial spasm. Even in contrast to these patients, who suffer from similar motor symptoms in the absence of changes in the central nervous system, blepharospasm patients committed an increased number of integration errors. WCST performance deficits in blepharospasm were accompanied by attenuated amplitudes of the P3a (Lange, Seer, Salchow et al., 2016). However, in contrast to the results from patients with PD, P3a alterations in blepharospasm were confined to the waveforms elicited by informative first repeat feedback cues. First repeat feedback cues typically evoke larger P3a amplitudes than later repeat feedback cues, but in patients with blepharospasm, this enhancement of P3a amplitudes failed to materialize. The enhancement of P3a amplitudes by first repeat feedback cues has been attributed to the comparatively large amount of rule uncertainty that is reduced by the presentation of these feedback cues (Kopp & Lange, 2013; Lange, Seer, Finke, 2015). Following the presentation of a shift cue, participants completing the cWCST are uncertain about which of the two remaining rules is the newly correct one. First repeat feedback cues eliminate this uncertainty and thus play a critical role in the process of rule inference on the cWCST. However, first repeat feedback cues differ from

repeat feedback cues that occur at a later point within a series of rule repetitions on at least one additional dimension. A first repeat feedback cue is necessarily presented after participants have encountered a shift feedback cue on the previous trial. First repeat trials thus involve a change in the presented cues from the previous trial (initiated by a shift cue) to the current trial (initiated by a repeat cue). This cue change differentiates first repeat feedback cues from later repeat feedback cues, which are always associated with a cue repetition (Forstmann, Brass, & Koch, 2007). While the incongruence between the type of cue transition (i.e., changing) and the type of the required rule transition (i.e., repeating) on first repeat trials may be associated with subtle performance cost on the cWCST (Barceló et al., 2002), it cannot fully account for the typically observed enhancement of P3a amplitudes. In a study involving healthy young participants, we observed increased P3a amplitudes not only after first repeat feedback cues, but also after second shift feedback cues that enabled participants to rule out all but one possible cWCST rule (Kopp & Lange, 2013). The fact that both first repeat feedback cues and second shift feedback cues eliminate rule uncertainty supports our notion that the enhancement of P3a amplitudes observed after informative feedback cues reflects processes of rule inference. Hence, we regard the specific reduction of P3a amplitudes in patients with blepharospasm after informative repeat feedback cues to be indicative of deficient rule inference in this clinical population. In sum, our two studies revealed alterations in rule inference in blepharospasm that appear to be related to the pathophysiology underlying this form of primary dystonia rather than to symptom-related distraction.

(please insert Table 2 about here)

4.4 Comparison and Integration

From a between-study comparison (Table 2), it becomes apparent that blepharospasm is the only neurological condition studied here whose cWCST performance profile is not characterized by an increased number of perseverative errors. The number of perseverative

errors is considered to be the WCST measure most closely related to cognitive set shifting or cognitive flexibility (Hartman et al., 2001; see also Figure 4). Hence, the analyses of erroneous responses on the cWCST suggest that WCST performance deficits in PD and ALS can indeed, at least in part, be attributed to impairments in cognitive flexibility. In contrast, deficient WCST performance in patients with blepharospasm (and possibly other forms of primary dystonia) might not be a sign of cognitive inflexibility but rather of disturbed rule inference (as indicated by an increased number of integration errors).

Within-study comparisons in our studies on primary dystonia confirmed that the number of integration errors was significantly more affected in blepharospasm than other cWCST error measures. It is important to note that most of the other within-study dissociations depicted in Table 2 are solely based on the lack of a significant group difference in one of the cWCST measures. For example, in PD, the number of integration errors was not significantly increased in comparison to healthy controls, but this does not imply that the number of integration errors was significantly less affected by PD than the number of perseverative errors or the number of set-loss errors. Similarly, the between-study dissociations suggested by Table 2 are only indirect. Patients with PD, ALS, and primary dystonia have not been contrasted directly within the same study, and the assessment and analysis of cWCST performance differed slightly between studies. For example, the number of examined PD patients was larger than the number of examined ALS patients, and PD patients completed an optimized version of the cWCST that involved considerably more trials. Hence, it is possible that, in fact, both PD and ALS are associated with an increase in the number of set-loss errors, but only the PD study had sufficient statistical power to detect this relationship. Therefore, differences across individual cells in Table 2 should not be misinterpreted as displaying conclusive evidence for robust dissociations or double dissociations of cWCST performance. Nonetheless, Table 2 indicates that some fairly distinct profiles of cWCST deficits emerge from the integration of the behavioral and

electrophysiological findings observed in the clinical studies. As detailed below, these profiles might be attributable to the neurophysiological changes underlying the different neurological conditions.

The observation of attenuated P3a amplitudes in both PD and blepharospasm points to the potential relevance of frontostriatal-loop integrity for the generation of the P3a. Both disorders have been related to alterations in frontostriatal circuits (Mink, 1996, 2003; Rodriguez-Oroz et al., 2009; Zoons et al., 2011), and the P3a might provide a window onto the functional status of these circuits (Solís-Vivanco et al., 2015). On the cognitive level, frontostriatal alterations seem to result in deficient attentional orienting, potentially giving rise to impaired WCST performance in both PD and blepharospasm. However, based on the present results, it appears that attentional alterations in PD and blepharospasm are qualitatively different. In blepharospasm, P3a alteration specifically affected the waveforms elicited by informative feedback cues, indicating that these patients might have difficulties directing attentional resources to those stimuli that allow inferring the correct rule on the WCST (Lange, Seer, Finke et al., 2015). In PD, P3a attenuation was generalized, affecting informative and non-informative feedback stimuli alike. One possible explanation for this difference might be that different elements of the executive frontostriatal circuit or different pathways within the basal ganglia are affected in PD and primary dystonia (Mink, 2003; Stoessl, Lehericy, & Strafella, 2015; Wichmann & DeLong, 1996). Alternatively, as a result of progressive neurodegeneration (Braak, Rüb, Jansen Steur, Del Tredici, & de Vos, 2005), specific frontostriatal alterations might be accompanied by widespread cortical dysfunctions in some patients with PD. This interpretation is supported by two observations: First, in contrast to patients with blepharospasm, cWCST performance deficits in PD were not confined to a particular error type. Patients with PD committed both more perseverative errors and more set-loss errors than healthy controls and the magnitude of the group difference did not differ as a

function of error type. Second, cWCST performance was only substantially impaired in those PD patients who showed attenuated amplitudes of both the P3a and a PSP-like potential. While the P3a might originate in cortico-subcortical brain networks (i.e., the executive frontostriatal circuit), the PSP has been related to activity in cortico-cortical networks (i.e., the frontoparietal executive network, Karayanidis et al., 2010). Hence, it is possible that in blepharospasm, specific frontostriatal alterations give rise to relatively circumscribed cognitive changes, whereas the combination of frontostriatal and cortico-cortical dysfunctions results in a wider spectrum of cognitive symptoms in a subgroup of patients with PD.

The frontoparietal circuits underlying PSP generation appear to be affected in ALS as well. PSP attenuation in ALS was observed in two independent studies using different paradigms. In addition, neuroimaging studies have revealed ALS-related alterations in frontoparietal connectivity (Agosta et al., 2013; Tedeschi et al., 2012). These connectivity changes have also been shown to be related to WCST performance (Agosta et al., 2013), suggesting that the executive dysfunctions observed in many ALS patients may be partly due to alterations in frontoparietal brain networks. The extent of these alterations seems to be markedly specific to ALS, as patients with blepharospasm as well as the vast majority of PD patients showed PSP deflections that did not differ in amplitude from those recorded in healthy controls. Note that the evidence for frontoparietal contributions to WCST deficits in ALS does not imply that possible frontostriatal dysfunctions (e.g., Bede et al., 2013) are irrelevant. In fact, P3a amplitudes seemed to be affected in ALS as well, but the empirical support for this finding was not as strong as the one for attenuated PSP amplitudes (Lange, Vogts et al., 2016).

In sum, we found PD, ALS, and blepharospasm to be associated with fairly distinct profiles of cWCST deficits. Neurodegenerative changes in frontoparietal cortical networks appear to disrupt the neural substrates of cognitive set shifting in ALS. The integrity of these frontoparietal networks (as indexed by the PSP) seems to be relatively spared in patients with

blepharospasm. In these patients, WCST performance deficits might rather result from dysfunction in the frontostriatal circuits supporting proactive attentional orienting for rule inference (as indexed by the P3a). Finally, in patients with PD, frontoparietal and frontostriatal alterations appear to interact in contributing to impaired performance on the WCST. These findings suggest that different neurophysiological changes can give rise to WCST performance deficits and that these deficits are most pronounced when multiple neural networks are affected.

5. Clinical Implications

A detailed understanding of WCST performance in patients with neurological disorders is of considerable relevance for several facets of clinical management. In the case of ALS, it has been shown that deficits on tests of executive functioning (such as the WCST) are related to reduced adherence to treatment and shortened survival (Chiò et al., 2012; Elamin et al., 2015; Montuschi et al., 2015). In patients with PD, the presence of executive dysfunction appears to predict progression to Parkinson's disease dementia (PDD; Janvin, Aarsland, & Larsen, 2005; Levy et al., 2002; Mahieux et al., 1998; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). To illustrate, PD patients who developed PDD one year later had been observed to commit about 60 % more perseverative errors than carefully matched control patients who did not develop PDD (Woods & Tröster, 2003). In addition, independent functioning in daily life might be particularly impaired in patients with executive dysfunction. These patients may, for example, have difficulty planning the complex movement sequences that are required for many everyday tasks (Merrilees, Klapper, Murphy, Lomen-Hoerth, & Miller, 2010). Such impairment in everyday functioning might also account for the observed relationship between executive dysfunction and reduced quality of life in patients with PD (Kudlicka, Clare, & Hindle, 2014). Finally, the burden perceived by caregivers of patients with PD (Kudlicka et al., 2014) or ALS (Burke, Elamin, Galvin, Hardiman, & Pender, 2015; Chiò et al., 2010) has been found to be increased when the patient's motor symptoms were accompanied by executive

deficits. Hence, executive impairment seems to be associated with negative consequences not only for patients but also for their caregivers. In the following, we will briefly outline how the results of our studies may inform the clinical care of patients with neurological disorders.

5.1 Implications of Differential cWCST Profiles in PD, ALS, and Primary Dystonia

The studies reviewed above suggest that overt WCST performance deficits in PD, ALS, and primary dystonia might have different cognitive and neural underpinnings. This finding implies that any intervention approach designed to remedy executive dysfunction in one of the three disorders should be tailored to the particular disorder at hand. Consider, for example, a possible clinical intervention based on the knowledge about WCST deficits in PD: In line with previous investigations using the WCST (Kudlicka et al., 2011), PD patients committed more perseverative errors in Study 4, indicating that PD-related deficits are at least partly due to set-shifting impairment and thus to cognitive inflexibility. Cognitive flexibility is thought to depend on the availability of dopamine in the striatum (Cools, 2006). Hence, it can be expected that replacement of striatal dopamine should improve WCST performance in patients with PD. In contrast, WCST deficits in patients with primary dystonia appeared to be related to impaired rule inference (as indexed by an increased number of integration errors) rather than to cognitive inflexibility. As striatal dopamine levels should be relatively unaffected in these patients (see also Albanese & Lalli, 2012), treatment approaches that aim at improving WCST performance by increasing the amount of dopamine in the striatum might be less efficient in primary dystonia than in PD. In fact, increasing dopamine in a non-dopamine-depleted brain area might even impair the cognitive functions associated with this area (Cools, 2006; MacDonald & Monchi, 2011; Seer, Lange et al., 2017). Instead, WCST performance in patients with primary dystonia may be ameliorated by cognitive training (Hindle, Petrelli, Clare, & Kalbe, 2013). As WCST deficits in primary dystonia are related to disturbed rule inference (Lange, Seer, Dengler et al., 2016; Lange, Seer, Salchow et al., 2016) and rule inference seems to depend on working

memory capacity (Lange, Kröger et al., 2016), these interventions might be particularly promising if they target working memory functions (Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006). At this point, it would certainly be premature to conclude that the proposed dissociations of cWCST performance profiles provide the most appropriate background for assigning groups of patients to personalized interventions. However, the present results provide a more detailed understanding of WCST deficits in PD, ALS, and primary dystonia, which may stimulate the development and evaluation of disease-specific intervention techniques in the future.

5.2 Implications of ERP Alterations in PD, ALS, and Primary Dystonia

Each of the investigated groups of patients showed alterations in at least one of the assessed ERP amplitude measures. These ERP measures (i.e., the P3a and the PSP) likely relate to distinct cognitive processes that are required for successful WCST performance (Figure 4). Moreover, across individuals, the amplitudes of P3a and PSP seem to be associated with performance on the cWCST (Lange, Seer, Loens et al., 2016) and other neuropsychological tests of executive functioning (Lange, Vogts et al., 2016). Although these relationships should be interpreted with caution due to small sample sizes and lack of consistent replication (Lange, Lange et al., 2016), they illustrate the potential utility of ERPs for assessing meaningful indicators of executive functioning (see Iyer et al., 2017, for a related approach). In contrast to conventional neuropsychological tests, ERP recordings involve substantially reduced motor demands. For example, both the P3a and the PSP are elicited by task cues that afford cognitive operations (i.e., attentional orienting/rule inference and set shifting) while not requiring overt movement. Assessment of these ERP indicators may thus be particularly useful in the diagnosis of cognitive status in patients with PD, ALS, and dystonia, where motor symptoms are likely to distort the results of neuropsychological testing (Goldstein & Abrahams, 2013; Raggi, Iannaccone, & Cappa, 2010; Seer et al., 2015; Seer, Joop et al., 2017).

In some cases, ERPs might also be more sensitive to subtle cognitive changes than neuropsychological tests. In our study using a simplified set-shifting paradigm (Lange, Lange et al., 2016), PSP amplitudes were observed to be attenuated in patients with ALS who did not show impairment on neuropsychological tests of executive functioning. This ALS-related reduction in PSP amplitude may indicate that set-shifting processes are altered in ALS, but as long as these alterations are confined to a single cognitive domain, they do not become apparent on behavioral performance measures. Nonetheless, it is possible that attenuated PSP amplitudes are a risk factor for the development of overt executive dysfunction later during the course of the disease. Once neural alterations are no longer restricted to a single system (e.g., to the frontoparietal network underlying PSP generation), they may be sufficiently severe to be detected as impairment in neuropsychological assessment. This hypothesis is further supported by our observation that the number of perseverative errors in patients with PD was only increased when both the amplitude of the PSP and the amplitude of the P3a were attenuated (Lange, Seer, Loens et al., 2016). Hence, these electrophysiological findings suggest that the prognosis of cognitive change in neurodegenerative diseases might be improved by the assessment of ERP measures. PSP recordings in particular seem to be a promising tool for the detection of developing executive dysfunctions in ALS and possibly PD.

In this context, it is also worth noting that the amplitude of the P3a elicited by informative feedback cues on the cWCST was found to be correlated to disease duration, both in PD and in blepharospasm (Lange, Seer, Loens et al., 2016; Lange, Seer, Salchow et al., 2016). These findings are in accordance with a previous study that concluded the P3a to be a possible marker for progressing frontostriatal dysfunction (Solís-Vivanco et al., 2015; see also Seer, Lange, Georgiev, Jahanshahi, & Kopp, 2016). If future studies corroborate the utility of P3a as an indicator of frontostriatal integrity, P3a recordings might contribute to the diagnosis and monitoring of PD and primary dystonia. At present, ERP correlates of cognitive processes

615 do not play a prominent role in the clinical assessment of neurological disorders (Altenmüller
616 et al., 2005). However, the promising results of our studies illustrate that ERPs can provide
617 useful and easily accessible information about the functional status of patients with PD, ALS,
618 and primary dystonia.

619 ## 6. Outlook

620 The present findings and their limitations highlight a number of opportunities to further
621 improve our understanding of WCST performance deficits in clinical conditions. First, our
622 study on WCST deficits in PD illustrates the potential of focusing on interactive contributions
623 of cognitive WCST components to overt WCST performance. Here, attentional deficits (as
624 indicated by attenuated P3a amplitudes) were fairly irrelevant for behavioral performance in
625 the absence of set-shifting deficits (as indicated by attenuated PSP amplitudes). PD patients
626 only committed an increased number of perseverative errors when the ERP indicators of both
627 cognitive processes, attentional orienting and set shifting, were affected. Including the
628 interaction term in this analysis substantially improved the prediction of cWCST performance
629 deficits in PD. Future studies on the processes underlying WCST performance deficits in
630 clinical populations should therefore consider the possibility that the contributions of some
631 factors might be non-additive.

632 Second, another one of our studies (Lange, Seer, Dengler et al., 2016) demonstrated the
633 benefits of using a clinical control group when revealing WCST impairment in blepharospasm
634 in comparison to a facial nerve disorder of different origin. Such comparisons reduce the
635 confounding impact of many disease-unspecific factors (e.g., depression, symptom-related
636 distraction, expectancies) and thus allow for a less ambiguous mapping of a deficit in a
637 particular WCST component to a particular pathophysiological change. In addition, as indicated
638 above, more direct comparisons between different disorders are required to arrive at reliable
639 disease-specific profiles of cognitive deficits (cf. Table 2).

Third, in order to arrive at a better understanding of the neural substrates of cognitive WCST components, it may be beneficial to directly correlate ERP and performance indicators of these components with imaging measures of neural network activity or connectivity (Jamadar, Hughes, Fulham, Michie, & Karayanidis, 2010). In particular, simultaneous EEG and fMRI recordings (Ullsperger & Debener, 2010) may shed new light on the neural mechanisms recruited while healthy participants or neurological patients complete the WCST.

Along similar lines, deep brain stimulation studies targeting the basal ganglia might be informative with regard to the contributions of frontostriatal circuits to cognitive flexibility on the WCST. In this context, it might be especially interesting to compare stimulation of the globus pallidus internus (GPi) and the subthalamic nucleus (STN). Stimulation of these basal regions has previously been shown to have dissociable effects on the number of perseverative and non-perseverative errors committed on the WCST (Jahanshahi et al., 2000, 2014; Pillon et al., 2006). Hence, examining the impact of GPi and STN stimulation on the cognitive components of WCST performance promises to further clarify how frontostriatal circuits give rise to cognitive flexibility.

Finally, the comparative analysis of P3a and PSP deflections conducted throughout the reviewed studies is certainly not the only possible approach to decomposing the electrophysiological correlates of cWCST performance. The use of time-frequency analyses of oscillatory EEG activity (Cooper, Darriba, Karayanidis, & Barceló, 2014; Cunillera et al., 2012; Prada, Barceló, Herrmann, & Escera, & 2014) or the application of information theory models to the study of P3-like potentials elicited during the cWCST and related paradigms (Barceló & Cooper, in press, Barceló, Periáñez, & Nyhus, 2007; Barceló et al., 2006; Kopp & Lange, 2013) may offer incremental insights into the neural basis of WCST deficits in clinical populations.

7. Conclusion

The cognitive symptoms of PD, ALS, and primary dystonia (and many other disorders) involve moderate performance deficits on the WCST. Although this finding seems to indicate a similar form of cognitive impairment common to all three neurological disorders, this similarity is only superficial. Observable WCST performance deficits might be caused by changes in a number of different cognitive processes. The detailed analysis of dissociable ERP and error measures provides a means to disentangle the complex relationship between these processes and thus to isolate some of the cognitive components of WCST performance. This methodological approach allowed identifying fairly distinct disease-related profiles of cWCST deficits in PD, ALS, and primary dystonia. WCST impairments in these disorders seem to relate to alterations in different cognitive processes (attentional orienting/rule inference vs. cognitive set shifting) that may be linked to changes in different (frontostriatal vs. frontoparietal) neural networks. Moreover, the electrophysiological correlates of these changes might serve as objective indicators of cognitive status or disease progression in PD, ALS, and primary dystonia.

In combination, the findings reported here illustrate how the study of executive functioning and cognitive flexibility can benefit from the integration of neuropsychological and psychophysiological approaches. Ultimately, the insights generated within such a framework may inform not only the understanding, but also the diagnosis and prediction of executive dysfunctions in neurological disorders.

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Tables

Table 1.

Disease characteristics of the neurological disorders investigated in our studies

	Parkinson's disease	Amyotrophic lateral sclerosis	Primary dystonia
Prevalence in Europe	108 to 257 per 100,000 persons[1]	5.4 per 100,000 persons[2]	15.2 per 100,000 persons[3]
Main motor symptoms	bradykinesia, rigidity, tremor, postural instability[4]	muscle weakness, muscle atrophy, paresis, spasticity, brisk reflexes[5]	twisting or repetitive movements, abnormal postures[6]
Proposed mechanism underlying motor symptoms	dopamine depletion in the dorsal striatum following the degeneration of dopaminergic neurons in the substantia nigra pars compacta[7]	degeneration of upper and lower motor neurons[5]	subtle alterations in the neural circuits connecting the basal ganglia, thalamus, sensorimotor cortex, and cerebellum[8]
Cognitive symptoms	Up to 31 % of the patients have Parkinson's disease dementia.[9]	Up to 15 % of the patients have frontotemporal dementia.[11]	no major deficits in intellectual ability, but some evidence

	About 67 % of the patients show cognitive impairment, predominantly in the domain of executive functioning.[10]	About 51 % of the patients show cognitive impairment, often in the domain of executive functioning.[11]	for executive impairment[12]
	dopamine depletion in dorsal striatum[13]		
Proposed mechanism(s) underlying cognitive symptoms	treatment-related dopamine overdosing in ventral striatum[13] extension of neurodegeneration to cortical areas[14]	extension of neurodegeneration to prefrontal cortical areas[15]	frontostriatal dysfunction[16] symptom-related distraction[12]

[1]von Campenhausen et al., 2005, [2]Chiò et al., 2013, [3]ESDE, 2000, [4]Jankovic, 2008, [5]Rowland & Shneider, 2001, [6]Fahn, 1988, [7]Kish, Shannak, & Hornykiewicz, 1988, [8]Zoons et al., 2011, [9]Aarsland, Zaccai, & Brayne, 2005, [10]Janvin, Aarsland, Larsen, & Hugdahl, 2003, [11]Ringholz et al., 2005, [12]Jahanshahi et al., 2014, [13]MacDonald & Monchi, 2011, [14]Braak, Rüb, Jansen Steur, Del Tredici, & de Vos, 2005, [15]Brettschneider et al., 2013, [16]Bugalho et al., 2008.

Table 2.

Profiles of cWCST deficits related to the neurological disorders investigated in our studies

	Behavior			Electrophysiology	
	PE	IE	SE	PSP	P3a
Parkinson's disease (Lange, Seer, Loens et al., 2016)	increased	unaffected[a]	increased	unaffected	attenuated[b]
ALS (Lange, Lange et al., 2016; Lange, Vogts et al., 2016)	increased	increased	unaffected[a]	attenuated	unaffected[c]
Blepharospasm (Lange, Seer, Denger et al., 2016; Lange, Seer, Salchow et al., 2016)	unaffected	increased	unaffected[a]	unaffected	attenuated[b]

Note. "Increased" and "attenuated" indicate that the respective cWCST measure (column) is significantly altered in the respective study population (row) in comparison to matched healthy control participants, $p < .05$. "Unaffected" indicates that the respective measure did not differ significantly between the respective study population and matched healthy controls. cWCST = computerized Wisconsin Card Sorting Test, ALS = amyotrophic lateral sclerosis, PE = perseverative errors, IE = integration errors, SE = set-loss errors, PSP = posterior switch positivity.

[a]The corresponding data were not reported in the original publications.

[b]P3a amplitude attenuation was specific (i.e., restricted to informative feedback stimuli) in patients with blepharospasm but non-selective in patients with PD.

[c]In a post-hoc analysis excluding participants who repeatedly switched rules in the absence of shift cues, P3a amplitudes were significantly attenuated in ALS patients.

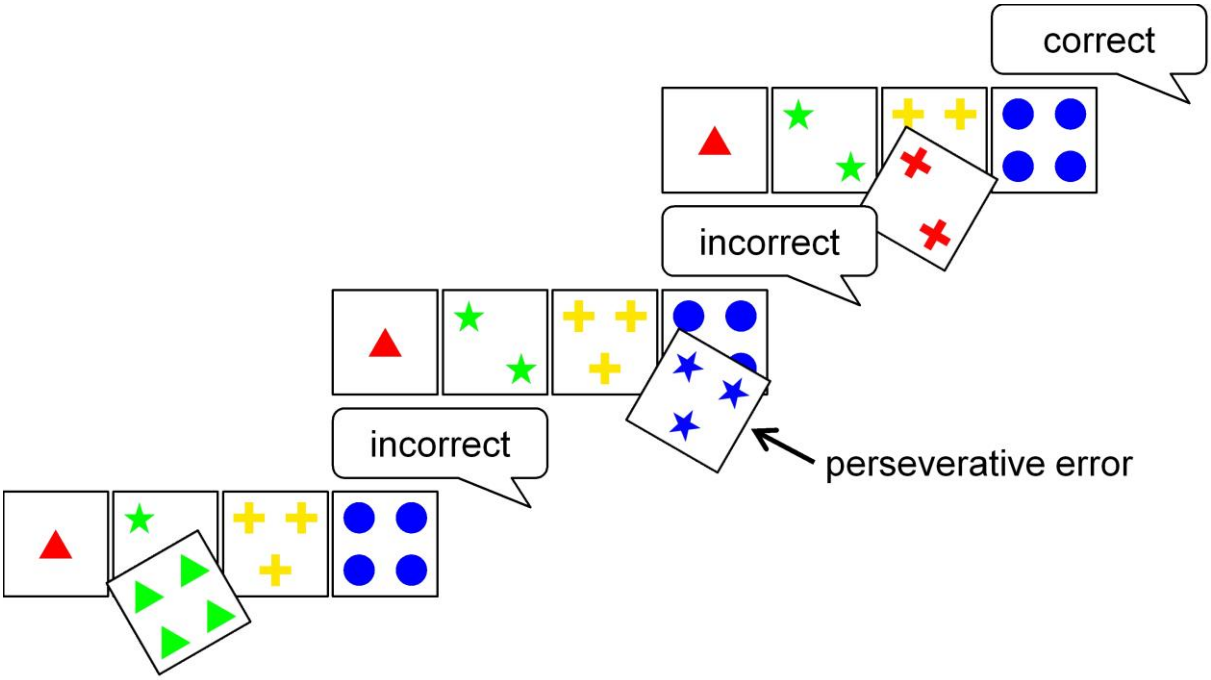


Figure 1. Three successive trials on the Wisconsin Card Sorting Test (WCST). In this particular scenario, an examinee receives negative feedback from the examiner after matching the cards according to the color rule on the first trial. Despite being informed that the color rule is not valid at the moment, the examinee does not shift to a different rule on the next trial (i.e., she or he commits a perseverative error). Finally, by matching the cards according to the shape of objects, the examinee applies a different rule on the third trial. This rule is currently valid as indicated by positive feedback provided by the examiner.

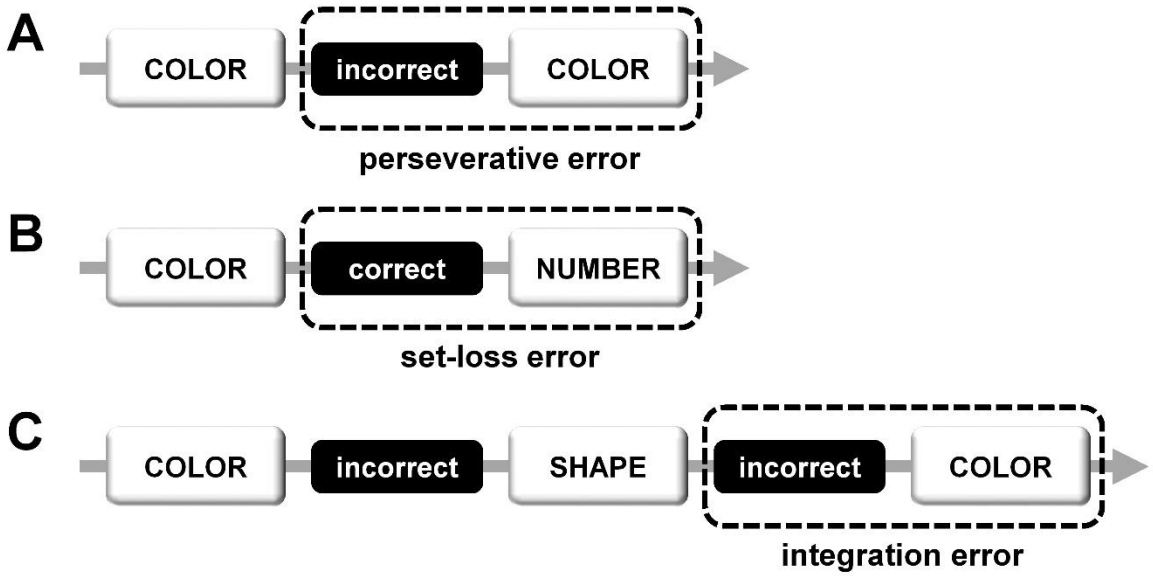
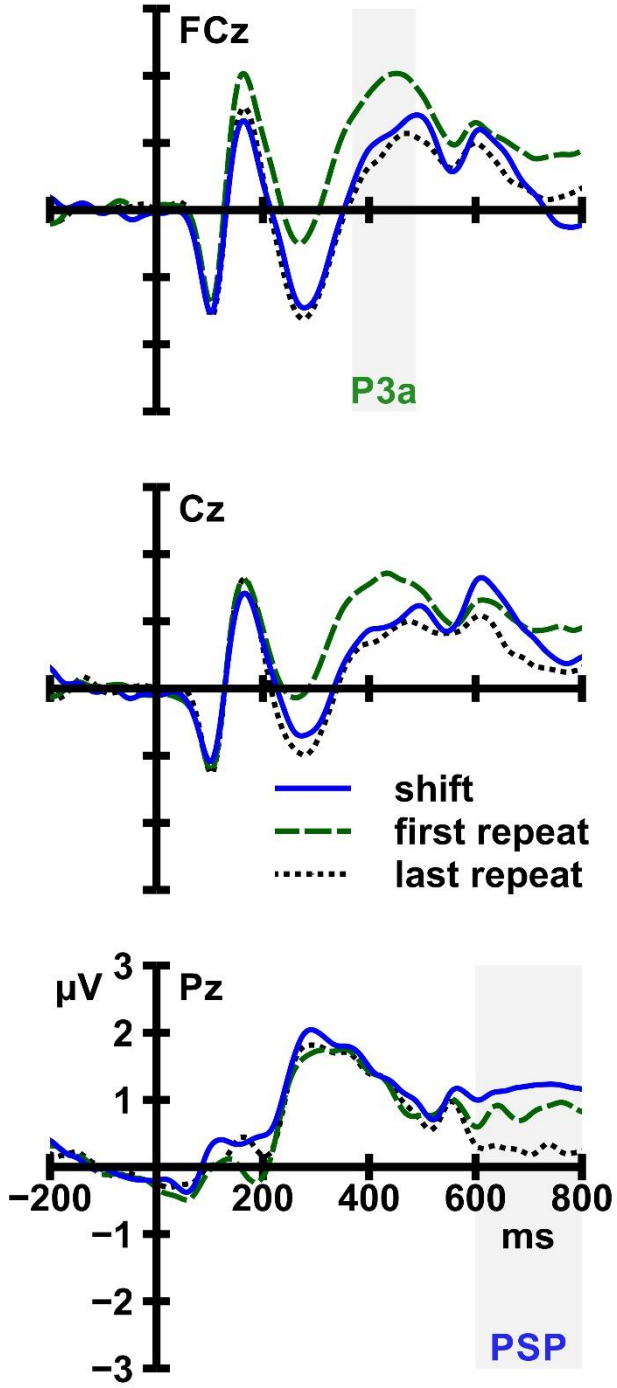


Figure 2. Behavioral correlates of cognitive processes underlying performance on the computerized Wisconsin Card Sorting Test. Note that in our clinical studies, the feedback cues "incorrect" and "correct" were replaced by the German words for "SWITCH" and "REPEAT". (A) A perseverative error is scored when an examinee continues sorting by a rule after negative feedback has signaled that this rule is not correct. Perseverative errors are considered to indicate deficient cognitive set shifting. (B) A set-loss error is scored when an examinee switches to another rule although positive feedback has signaled that the previous rule needs to be repeated. Set-loss errors are considered to indicate deficient set maintenance. (C) An integration error is scored when, after a change in task rules, an examinee fails to integrate the information about the previously applied rules, i.e., when a rule is applied that could have already been eliminated. Integration errors are considered to indicate deficient rule inference.



22

23 *Figure 3.* Event-related potential (ERP) correlates of cognitive processes underlying
24 performance on the computerized Wisconsin Card Sorting Test. The frontocentrally distributed
25 P3a is considered to reflect the neural processes underlying attentional orienting for rule
26 inference. The amplitude of the P3a is usually larger after informative first repeat cues than

after repeat cues that occur later in a series of rule repetition. The parietally distributed posterior switch positivity (PSP) is considered to reflect the neural processes underlying cognitive set shifting. PSP refers to the difference in late parietal ERP activity between shift and repeat cues. The absolute level of ERP activity in the PSP analysis window has also been referred to as sustained parietal positivity (Lange, Seer, Loens et al., 2016; see also Wylie, Javitt, & Foxe, 2003) or cue-locked positivity (Karayanidis et al., 2010). This deflection has sometimes been linked to the P3b component (Barceló et al., 2002; Kopp & Lange, 2013; see Karayanidis & Jamadar, 2014, for discussion). The figure (reprinted with permission) displays grand average ERP data from $N = 34$ healthy controls (mean age = 62.5 yrs) participating in the study reported in Lange, Seer, Salchow, and colleagues (2016).

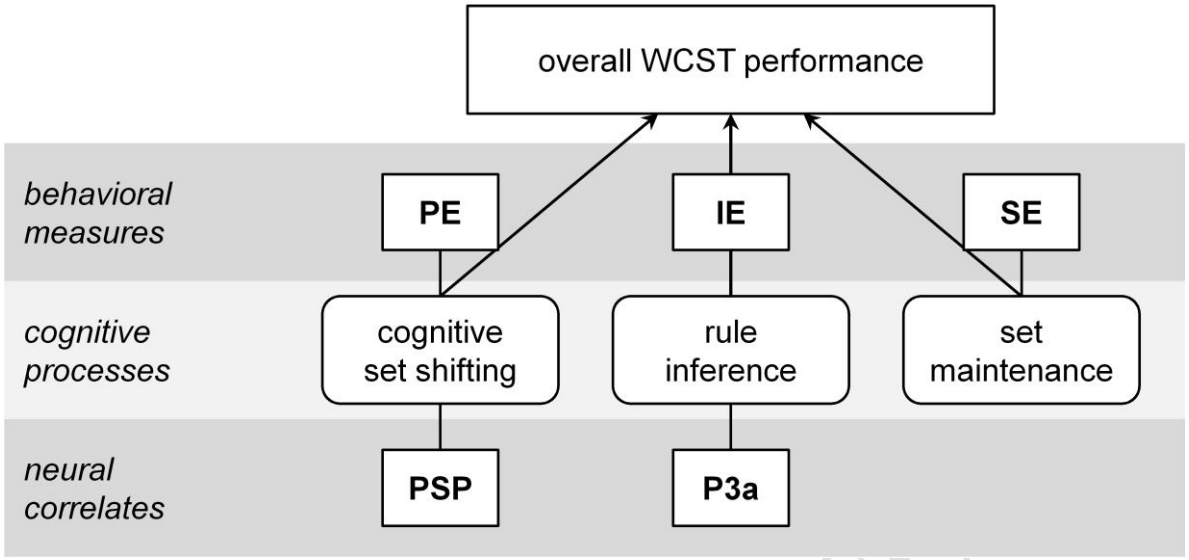


Figure 4. Overview of the cognitive components of performance on the Wisconsin Card Sorting (WCST) and their behavioral and electrophysiological manifestations on the computerized WCST. Rounded shapes indicate latent constructs; rectangles indicate observable indicators. PE = perseverative errors, IE = integration errors, SE = set-loss errors, PSP = posterior switch positivity.