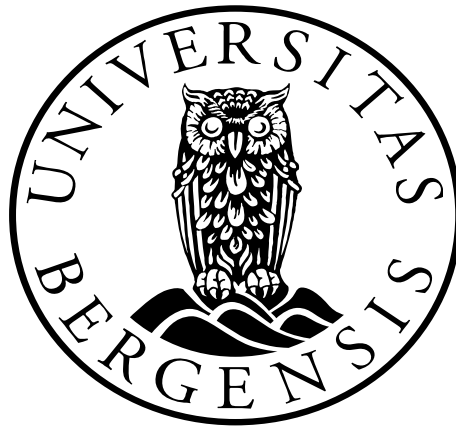


*A Frontoparietal Network Underlies
both the Standard and an Auditory
Adaptation of the WCST*

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Abstract

The executive functions are crucial for leading a deliberate life which delicately balances the considerations posed by ourselves and our surroundings. Several of the most common mental illnesses impact executive functions. In order to develop effective treatments, efficient and reliable ways of measuring executive functioning are required. One of the most popular tests of executive function is the Wisconsin Card Sorting Test (WCST), which has been proposed to challenge a range of functions, including working memory, cognitive flexibility, and making logical inferences. An fMRI-study was done to investigate the neural substrate for performing the WCST, alongside a newly developed auditory adaptation of the test for use with the visually impaired. A high-level control condition where the sorting rule was disclosed was used, in an attempt to sift out working memory storage functions from manipulation and hypothesis generating functions. Contrasting the visual test with the auditory one revealed activation limited to the sensory cortices. Contrasting the tests with the high level control condition revealed a frontoparietal network including the frontal eye fields and the intraparietal sulci. These results highlight the importance of a distributed network of brain areas for solving the WCST, which is not limited to the frontal cortex. In addition, the lack of a difference between the WCST and the Auditory Sorting Task outside of the sensory cortices supports the application of the AST as a substitute for the WCST in the visually impaired population.

Keywords: fMRI, wisconsin card sorting test, executive functions, dorsal attention network

Sammendrag

De eksekutive funksjoner er avgjørende for en gjennomtenkt livsførsel som nennsomt ivaretar både ens egne og ens omgivelers hensyn. Flere av de vanligste mentale lidelser forstyrrer eksekutive funksjoner. For å utvikle effektive behandlingsformer, er det nødvendig med pålitelige og kostnadseffektive måter å måle eksekutiv fungering på. En av de mest populære tester av eksekutiv fungering er Wisconsin Card Sorting Test (WCST), som er blitt sagt å utfordre en rekke funksjoner, inkludert arbeidsminne, kognitiv fleksibilitet og det å trekke logiske slutninger. En fMRI-studie ble gjort for å undersøke det nevralt grunnlaget for utførelsen av WCST, i tillegg til en nylig utviklet auditiv tilpasning av testen til bruk med synshemmede. En kontrollbetingelse der sorteringsregelen ble oppgitt ble brukt, i et forsøk på å sile ut lagringsfunksjoner i arbeidsminne fra bearbeidende og hypoteseproduserende funksjoner. Ved sammenlikning av den visuelle testen med den auditive, ble det avslørt aktivering begrenset til de sensoriske barker. Ved sammenlikning av testene med kontrollbetingelsen, ble det avslørt aktivering i et frontoparietalt nettverk som innbefattet de frontale øyefelt og de intraparietale furer. Disse resultatene understreker viktigheten av et utstrakt nettverk av hjerneområder for utførelsen av WCST, som ikke er begrenset til frontallappen. I tillegg støtter fraværet av ulikhet mellom WCST og Auditory Sorting Task ut over de sensoriske barker bruken av AST som erstatning for WCST i den synshemmede befolkning.

Nøkkelord: fMRI, wisconsin card sorting test, eksekutive funksjoner, dorsale oppmerksomhetsnettverk

Preface

When Professor Karsten Specht asked me if I would like to analyse some fMRI-data of an experiment using the Wisconsin Card Sorting Test, I was excited about getting some hands-on experience with neuroimaging data. However, the theory surrounding the construct “executive functions”, and the epistemological issues about drawing inferences about mental functions from performance on a test, were quite overwhelming. Although I’ve learned about many interesting lines of research – and many of these revealed a convergence, which always fascinates me – the field still seems enormous to me. Luckily, I had the practical processing and analysis of the data to relax with when the literature got too hairy.

The experiment that this thesis is based on was designed and performed by Professor Specht and colleagues, but the data were left untreated for reasons not disclosed to me. As I knew next to nothing about the handling of this type of data, I was surprised to find that the procedure was really quite straightforward. The software tool, SPM, allows for much more customisability than is usually presented in the guides, though, and so some experimentation was required for me to fully grasp when to do what. When I had tried my hand on some example data, I went to PhD Candidate Justyna Beresniewicz to have my skills assessed. Although she said I had become proficient, she still graciously spent several hours tweaking the MATLAB code, in order to find a more efficient way for me to run the procedures.

When the final analyses were over, I was met with a new challenge: What do these images mean? This set off a long and arduous trek through the literature which I still feel I’ve only just started on. What especially caught my attention was how central motivation is to not only the executive functions, but also how the processes underlying motivation actually shape the perception of reality, such as in schizophrenia. This, however, was something of a trap, as the literature on schizophrenia turned out to be bottomless, and this experiment was not directly related to that particular subject.

In the end, I think I managed to pick out literature that sheds some light on what the executive functions are, why they matter, and some ways they can be studied. I know that there are several of the theoretical questions discussed in this paper that I will follow with great interest also after submission. The analyses, interpretation, and literature search that went towards this thesis were very much independently done by myself, with sparse but influential guidance provided by my supervisors.

I would like to thank my supervisor Professor Karsten Specht for his help throughout this process, and for his contagious intellectual enthusiasm. I would also like to thank PhD Candidate Justyna Beresniewicz for introducing me to SPM and for taking the time to work out original MATLAB-scripts for my benefit. I am also grateful to Kristiina Kompus for fluidly making the arrangements for me to get involved with this project. Finally, I wish to thank my loving and stalwart girlfriend, Maria Befring Hage, for emotional, critical, and alimentary support throughout this challenge.

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A Frontoparietal Network Underlies both the Standard and an Auditory Adaptation of the WCST

The executive functions are a set of psychological constructs that are thought to underlie the concerted use of cognition in the service of achieving goals. The ones that are generally included are self-control, interference control, working memory, and cognitive flexibility (Diamond, 2013). Many of them are characterised by how they primarily modulate other processes, rather than acting alone (Miller & Cohen, 2001). This can make testing them difficult, as they have to be inferred from how other functions are used (Miyake & Friedman, 2012).

Creating a plan might be an example of an activity where most, if not all, executive functions are needed (Owen, 1997; Tanji & Hoshi, 2001). Working memory and imagination are needed to envision the faraway goal which motivates the plan. They're also needed to think of all the necessary steps and contingencies towards that goal. Attention has to be controlled away from distractions and towards this activity and, by extension, the future. Self-control must be exerted to finish the plan and not give in to the temptations of doing more pleasant things instead. Planning – instead of acting on impulse – is probably what most defines these executive functions. They are there to guide behaviour towards goals not currently perceived, and to protect against dangers not yet encountered. (Casey et al., 2011; Rogers et al., 1999).

Though the term executive functions didn't become widely used until the seventies, the functions that this term refers to were studied previously. Short-term memory – distinct from the working variant according to some, but still a necessary component of it – was studied already in the 1950s by Miller (1956). The control of attention was proposed as a necessary faculty by Donald Broadbent in 1958. Posner and Petersen (1990) suggested later that there must be an “executive” attention system, and Baddeley and Hitch (1974) also

included a “Central Executive” in their model of working memory. Although there now is general agreement about what to call them as a group, the particular functions can sometimes be trickier to define (Holroyd & Yeung, 2012; Miller, 2013).

In the following sections, the executive functions will be described, together with the neural structures and/or processes thought to underlie them. Sometimes the same functions will go under different names, and sometimes different functions will go under the same name. Efforts have been made to disentangle some of these knots, but some confusion will probably remain. Afterwards, there will be a short review of the Wisconsin Card Sorting Test (WCST) and its applications. The last part of the introduction will describe the importance of dopamine to the executive functions, and how dopamine dysregulation is implicated in several conditions displaying as key symptoms problems with executive function. Then the present work will describe an experiment investigating on the one hand, a newly developed auditory adaptation of the WCST called the Auditory Sorting Task (AST), and on the other hand, the neural substrates underlying performance on the WCST. The results of this experiment will then finally be discussed in light of the disambiguations of the executive functions attempted in the introduction.

Working Memory

Memory could be defined as the ability to retain information in the absence of any external stimulus. The distinction between short-term and long term memory was shown in the case of Henry Molaison, formerly known by his initials H.M., who had crippling anterograde amnesia of long term declarative memory, but an intact short term memory after a bilateral lesion of the medial temporal lobes (Scoville & Milner, 1957).

According to Baddeley and Hitch (1974), working memory can be modelled as several sensory modality bound buffer components which “rehearse” whatever memories you’re

working with. There were originally two of these, *the phonological loop* which is made up of an ability to store memory traces of sound for a very short time and a rehearsal process similar to internal speech, and *the visuospatial sketchpad* which can hold a limited amount of objects and their visual and spatial features (Baddeley, 2003). A control system was hypothesized to allocate attention between these according to circumstance, termed *the central executive*. The division of working memory into different modalities was motivated by findings from dual task paradigms, where performing two tasks simultaneously would be more impaired if the tasks were in the same modality than if they were not (Baddeley & Hitch, 1974). The idea that memory could be divided in this way is supported by research on long-term memory, where recall of a memory in a certain modality is reflected in activity in the corresponding sensory cortex (Binder & Desai, 2011). However, working memory was in the earliest neuroscientific papers often localised to the frontal cortex (Fuster & Alexander, 1971; Goldman-Rakic, 1995; Cohen et al., 1997). Does this mean that the frontal cortex can represent information from any modality, or does it mean that working memory representations are more abstract? What those early studies typically reported was that there is sustained neural activity in the frontal cortex that corresponds to the delay in which the subject is holding something in memory before giving a response proving that the memory was retained (Fuster & Alexander, 1971; Goldman-Rakic, 1995; Cohen et al., 1997). The types of memories subjects typically are asked to hold could well be described as sparse. That is, they are positions (Goldman-Rakic, 1987), relations (Cohen et al., 1997), contingencies (White & Wise, 1999), rules (Wallis, Anderson, & Miller, 2001) and numbers (Paulesu, Frith, & Frackowiak, 1993). It may be that the frontal cortex only deals with sparse representations, or it could be that the sustained activity is somehow signalling to more posterior areas for them to in turn hold the complete representations (Miller & Cohen, 2001; Postle, 2006). Zeman et al. (2010) reported a case of such a dissociation between florid mental imagery and

abstract visuospatial representations, wherein the subject, MX, showed normal frontal activation, but abnormal activation in posterior cortex. Others have shown that working memory is not uniquely present in the frontal cortex. Warrington and Shallice (1969) reported that a young man who had suffered a stroke to his left parietal cortex, displayed a selective impairment of verbal working memory. Postle (2006) suggests that the short-term storage of information is actually subserved by more posterior areas of the brain, more specifically, the areas that are involved in the perception of the same kinds of information. In this regard, delay-period activity in the prefrontal cortex (PFC) might reflect a more managerial function, where it is biasing posterior cortex to prioritise the to-be-remembered information in some way (Corbetta & Shulman, 2002; Miller & Cohen, 2001). Said another way, the PFC could play the role of remembering what to remember. One could say that short-term memory interference effects of PFC disruption is support for this view (Chao & Knight, 1995; Thompson-Schill et al., 2002), but if the PFC is telling posterior cortex to remember something, and the PFC doesn't store information on its own, who is telling the PFC to tell posterior cortex to remember? In a lesion study by Petrides (2000), a double dissociation was observed where inferotemporal lesions disrupted retention, while dorsolateral PFC lesions disrupted the ability to monitor many items at once. This shows that posterior cortex is needed to retain information across a delay, while the dorsolateral PFC is not.

To summarize, short term memory was early shown to be something different than long term memory. It was hypothesized that short term memory was enacted by specific modules in the brain, like Baddeley and Hitch's (1974) components, or the frontal cortex. However, consecutive research has led to the assumption that short term memory can be performed by most parts of the cortex, and often by the same parts that are involved in perception in that modality. Nevertheless it is likely that some sort of control mechanism is

affecting what to be remembered, including areas in the frontal cortex (D'Esposito & Postle, 2015; Miller & Cohen, 2001).

Inhibition

The mind is able to imagine many courses of action at any single moment, yet the body is only able to do more or less one thing at a time. In order to choose the one thing to do, one has to be able to suppress all the other impulses one might have. This ability to suppress impulses underlies the very notion of making choices, as were we not able to put an action on hold, the choice would already have been made before we were done deciding. This could be why Miyake & Friedman (2012), in their factor analysis of executive functions, couldn't separate inhibition-specific variance from variance common to all the executive functions. That is, inhibition was found to be central to performance on all measures of executive functions.

The experience of being faced with a choice is captured in the term 'cognitive conflict'. The posterior medial PFC and the anterior cingulate cortex (ACC) have been linked to cognitive conflict and performance evaluation (Botvinick, Cohen, & Carter, 2004; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Activity in these areas increases prior to making a decision between two competing responses (overriding prepotent responses or underdetermined responses), and also after making a response that turns out to be wrong. It is hypothesized that these areas, either directly or through signals to neighbouring areas, adjust the amount of cognitive control that is expended on a task, depending on how well things are going (Botvinick et al., 2004).

Many different tasks where the inhibition of a response is needed regularly engage the ACC, like the flanker task (Pardo, Pardo, Janer, & Raichle, 1990), the go/no-go task (Braver, Barch, Gray, Molfese, & Snyder, 2001), and the Stroop Test (Botvinick, Nystrom, Fissell,

Carter, & Cohen, 1999). The Stroop Test (Stroop, 1935) has shown this frequently (MacLeod & MacDonald, 2000). In the Stroop Test, the subject is presented colour names one by one, in differently coloured ink. The objective is to pronounce the name of colour of the ink. It is regularly shown that people have more difficulty with this task when the presented colour name is written in an ink of a different colour.

Holroyd and Yeung (2012) propose that the ACC is involved in the hierarchical maintenance of goals and sub-goals, using these representations to evaluate different action-options within a broader context. Self-control involves comparing two or more options suspected of yielding reward, and choosing the option which yields the larger reward even though the other option seems more enticing (Holroyd & Yeung, 2012). How it's even possible for the brain to know that one option is more rewarding while at the same time representing a different option as seemingly more rewarding, is quite strange. Partly motivated by how lesions of the ACC can result in akinetic mutism (Németh, Hegedüs, Molnár, 1988), Holroyd and Yeung (2012) propose that the ACC is necessary to construe any extended behaviour as worthwhile. They argue that any action always takes some immediate effort, but that normally, this effort is justified by whatever longer term goals the action leads to. What the ACC does, according to Holroyd and Yeung (2012), is link the different action-options to the expected results, and compare the expected pay-off of each option.

Persons suffering from addiction seem to have problems with inhibiting whichever behaviour they're addicted to. The reason for this might be that their urges are stronger than other people's urges (Robinson & Berridge, 1993), or it might be that their ability to act contrary to their urges is weaker than in other people (Baumeister, Vohs, & Tice, 2007). The latter option could for example be a difference in a frontostriatal control network investigated by Liston et al. (2006). Both of those might be the case, and there is even a third possible factor. Persons with damage to the ventromedial PFC are afflicted by a severe bias towards

short-term gratification (Bechara, Damasio, Damasio, & Anderson, 1994), and many addicted individuals present with the same bias (Noël, Van der Linden, & Bechara, 2006). It is not that they can't imagine the future consequences of their actions, but it seems those imagined consequences don't influence their affect as they do for other people. If this is the case, then it is not really a problem of executive function, but a problem of motivation. They're acting rationally within the premises of their limited ambitions.

Also information can be inhibited. Patients with damage in PFC are impaired in a nonmatch-to-sample task where there are distracting stimuli in the delay (Chao & Knight, 1995). Attention is also a type of inhibition of information, as everything that is not attended to is ignored. Again, patients with damage in the lateral PFC show larger amplitudes in early event-related potentials (ERP) taken from sensory cortices, suggesting that they are left more open to outside interference (Knight, Hillyard, Woods, & Neville, 1981).

Rules and Cognitive Flexibility

Keeping track of and following the rules for behaviour is central to the functions of the executive system. Anyone can act goal-directed if there is ever only one goal, and no intermediate considerations to take into account. Let's say you are a five year old and want to buy ice cream. You could simply break the piggy bank and buy ice cream for the money inside, but then you'd get in trouble with your mother, and so you need to balance the two goals of buying ice cream and not getting in trouble with your mother. This is an example of how one's own goals place limitations on each other. Even if one only has one goal, limitations can be placed on it from the outside world. There might be a line to get ice cream. Now, you could fight the other kids to get ice cream right now, but then you might get grounded, and you wouldn't be able to buy ice cream the next day, so you wait for your turn. Navigating considerations like these is what the executive system is for. Behaving "correctly"

necessitates being aware of the different goals you have, while also being aware of the contexts that determine when pursuing them will be successful or not.

Following rules is something that engages every part of the executive system. To follow a rule, the minimum requirements are that you have one thing you want to do, while simultaneously being aware that it is not the right thing to do, i.e. you need to represent in your mind two thoughts at once. You also need to be able to inhibit your impulses until you have decided. Additionally, a rule is only in special cases always meant to be followed, which means a person needs to be able to adapt flexibly to changing circumstances. Finally, a rule is by definition a generalisation, dictating how to behave across many specific situations. Therefore, to follow a rule, one needs to be able to generalise from specific exemplars. Some studies providing insight into how these abilities are manifested in the brain follow below.

A combined match to sample and non-match to sample task that Wallis et al. (2001) used shows the learning of rules by single neurons in the PFC. Monkeys were trained to do two types of task, and had to perform either the one or the other, depending on which signal they were given. Wallis et al. (2001) showed that there were single neurons in the PFC which were selectively responsive to the rules determining which task to perform, independently of the stimulus features of the tasks and the rule-signalling cues.

One experiment done by Buschman, Denovellis, Diogo, Bullock, and Miller (2012) explored the mechanisms underlying several of the executive functions discussed above. Arrays of electrodes were placed in the dorsolateral PFC of macaque monkeys, while the monkeys were making rule based judgements. A cue would tell the monkeys to either attend to the colour of a stimulus or to the orientation of the stimulus. The stimulus could be one of two colours, and in one of two orientations. Depending on which colour or orientation he stimulus was in, the monkey was supposed to look to the left or to the right. One half of the electrode pairs registered, in the beta band, synchronous oscillations connected to the colour

rule, and the other half registered synchrony connected to the orientation rule. This suggests that the rhythm of neural activity plays a role in forming context-dependent ensembles out of a jumbled mass of neurons (Buschman et al., 2012). It was also found that after being cued to attend to colour, but before the stimulus had appeared, the ensemble that had showed synchrony connected to orientation was showing synchrony in the low-frequency alpha band. This effect, together with behavioural data showing an increased reaction time for the colour task compared to the orientation task, was interpreted as reflecting a need to suppress the orientation ensemble (Buschman et al., 2012).

Another experiment was done on category learning (Antzoulatos & Miller, 2011). Two images were made of a distribution of spots, and then several hundred versions of these were made by distorting the originals. These several hundred exemplars could thus be classified into one of two categories based on which prototype they originated from. Macaque monkeys were trained to look to either direction depending on which category it was presented. The monkeys would start learning only a few exemplars, so that the task could be solved by simple stimulus-response-learning. The number of exemplars would increase, however, so that by the end, the monkeys would have to have extrapolated the categories or they would fail. Electrodes were recording from the striatum and the PFC. What Antzoulatos and Miller (2011) found was that during the early trials, neural activity in the striatum was a better predictor of performance than activity in the PFC, but in the later trials, this relationship was reversed. In another study (Antzoulatos & Miller, 2014), where these data were reanalysed, it was found that, during the middle trials when the monkeys were starting to learn the categories, there was an increase in synchronous oscillations between the striatum and the PFC. Then, in the final trials, when the monkeys had mastered the categories, there was an increase in category-specific synchronous oscillations between the striatum and the PFC (Antzoulatos & Miller, 2014). Buschman and Miller (2014) take these results, together

with the results from Buschman et al. (2012), as an indication of synchronous oscillations being the substrate for cognitive flexibility and set shifting.

Maintaining task set and shifting task set sound like opposites. But the way these are tested suggests that they are more similar than they seem. The ability to maintain task set – or concentrate – is often tested by measuring performance in the face of distraction (Fenske & Eastwood, 2003) . The mechanisms behind this are generally described as inhibition of irrelevant stimuli or information. The ability to shift sets – or cognitive flexibility – is usually tested by giving alternating tasks, and measuring the switch cost – reductions in accuracy and increases in reaction time (Rogers & Monsell, 1995) – or the number of perseverative responses (Lacreuse, Parr, Chennareddi, & Herndon, 2018). Also in the case of flexibility are the mechanisms described as inhibition – inhibition of the previous task set. However, performance in concentration and flexibility often dissociate, with people performing well in one but not the other (Friedman, Miyake, Robinson, & Hewitt, 2011).

Buschman and Miller (2014) suggest that cognitive flexibility is supported by the mixed selectivity of neurons and their ability to dynamically form different ensembles among neurons that are all structurally connected. Siegel, Warden, & Miller (2009) propose that one way in which two or more ensembles can exist simultaneously without them collapsing into one, is by oscillating out of phase with each other.

Cognitive flexibility can be defined simply as the ability to shift sets, or it could mean something more comprehensive, involving the ability to reconfigure the relations among representations (Wiseheart, Viswanathan, & Bialystok, 2016). This ability might be subserved by dynamically forming networks as in the studies by Buschman et al. (2012) and Anzoulatos and Miller (2011; 2014).

Bilinguals regularly have to reconfigure the relations among representations when flexibly switching from one language to another. It's been observed that bilinguals exhibit an

enhanced concurrent activation of PFC and striatum in response to tasks requiring such reconfiguration (Becker, Prat, & Stocco, 2016). Becker and colleagues (2016) compared the performance of monolinguals and bilinguals on a cognitive flexibility task, and applied dynamic causal modelling to their functional magnetic resonance (fMRI) data. It was shown that in monolinguals, activation of the ACC led to reduced activity in the PFC and striatum, while in bilinguals activation of the ACC led to a small *increase* in prefrontal and striatal activity. In an earlier study by Prat and Just (2011), it was shown that in people with higher working memory capacity, difficult sentences elicit recruitment of the dorsolateral PFC and striatum. Wiseheart et al. (2016) found that bilinguals had an advantage in global switch costs, but not in local switch costs, compared to monolinguals. They argue that the local switch cost reflects simple task preparation more than online cognitive flexibility, and so they conclude that the advantage of bilinguals in global switch costs reflects an advantage in executive functions.

Attentional Control and Mind-Wandering

In 2002, Corbetta and Shulman proposed a model for explaining how attention is controlled in the brain. This model was partly based on earlier models by Posner and Petersen (1990), and Mesulam (1981). Earlier research (Desimone & Duncan, 1995) had shown that attention is a heightened state of activity in the neurons that code for whatever is being attended to, in the appropriate sensory (Heinze et al., 1994; Hillyard, Hink, Schwent, & Picton, 1973; Petkov et al., 2004), associative (O'Craven, Downing, & Kanwisher, 1999), or even hippocampal (Muzzio et al., 2009) parts of the brain. Ignoring something likewise is reflected in an inhibited, or lowered state of activity in the corresponding neurons (Mazaheri et al., 2014). In the face of changing goals or changing circumstances, what's important to focus on cannot be immutably hard-wired into us, but must be allowed to change with the

situation. The parts of the brain responsible for steering our focus in this way are, according to Corbetta and Shulman (2002), the superior parietal lobules, the intraparietal sulci (IPS) and the frontal eye fields (FEF), collectively called the Dorsal Attention Network (DAN). These areas work in concert to signal to sensory and associative areas of cortex to either increase or subdue their activity according to what it is most fitting to attend to at any given moment. It is thought that the IPS and the FEF contain priority – or salience – maps of the perceptual space a person at any given moment is inhabiting (Corbetta & Shulman, 2002), wherein the salience of stimuli is affected by a combination of their sensory intensity, learned and/or inborn behavioural relevance, and effortful top-down control signals.

Buschman and Miller (2007) suggest that the IPS is more involved with bottom-up attention and that the FEF are more involved with top-down, based on the temporal order they become active in the two types of tasks. Recording from several sites, including the FEF and the IPS, Buschman and Miller (2009) found that during visual search, the FEF displayed a serial activation pattern corresponding to the sequential way in which the animal looked through its visual field. This pattern of activity was not found anywhere else. These findings suggest that the FEF are directing the IPS during controlled search for a specific stimulus.

The control of attention seems to work both by enhancing the signals being attended to, and by inhibiting the irrelevant signals. Mazaheri et al. (2014) found that making a judgement about a stimulus in one modality, while ignoring the other modality, was associated with decreases of alpha power in the attended modality's cortex and increases of alpha power in the ignored modality's cortex. Marshall, O'Shea, Jensen and Bergmann (2015) demonstrated that alpha modulations in visual cortex in relation to attention tasks are caused by the FEF, when they effectively reduced these by applying transcranial magnetic stimulation to the contralateral FEF. Händel, Haarmeier and Jensen (2011) found that amount of alpha oscillations in occipital cortex correlated with successful inhibition of attention.

Subjects were attending to either the right or the left, and alpha oscillations in the unattended hemisphere predicted inability to report stimulus changes on that side. This effect was shown to be compromised in adults with attention deficit hyperactivity disorder (ADHD) (Ter Huurne et al., 2013). These findings suggest that successful allocating of attention depend not only on paying attention to the right things, but also on not paying attention to the wrong things. In addition, the close relationship between oscillations and cognition shows up again in attention research.

Buschman and Miller (2010) observed that shifts of attention were not only synchronised to a beta (25 Hz) rhythm, but also that each shift occurred within a single oscillatory cycle. In 2009, Siegel and colleagues found that neural ensembles reflecting two separate items held in working memory were oscillating out of phase with each other. Buschman and Miller (2010) speculate what possible benefits rhythmic oscillations could bring. Internal synchrony strengthens the integrity of an ensemble, while external synchrony could strengthen the effect that one ensemble has on its output targets through temporal summation. Also, if computations are done in discrete, phase-locked packets, then computations in one area that depend on computations in a different area can be done more efficiently, since the ensembles would «know» when the required computations will be ready (Buschman & Miller, 2010). These hypothetical effects of rhythmicity would benefit both local and network level processing.

In Womelsdorf and Everling (2015) the whole process of attentional control is described, from motivational and goal-setting computations in the PFC, striatum, and limbic structures, to salience maps, search directives, and polymodal spatial representations in the FEF, IPS and superior colliculus, before finally fully realising in feature-specific modulations in sensory cortices. Here it is also emphasised how synchrony between the different nodes of the network underlie the different effects of controlled attention, and indeed how synchrony

flexibly produces these networks. Since the salience maps of FEF and IPS depend on motivation, goals, and context, these must be able to rapidly update in correspondence with top-down signals.

This DAN had been showing up in several neuroimaging studies (Cabeza & Nyberg, 2000; Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999), together with a different network that seemed to be deactivating concurrently with the DAN's activating (Gusnard & Raichle, 2001; Fox et al., 2005). When performing blood-oxygen-level-dependent (BOLD) fMRI one needs to use a control condition – sometimes called a baseline or resting state – to compare with. Otherwise, the sustained activation in task-related areas would be impossible to interpret. However, because a living brain is always active (Raichle, 2006), not only is it hard to detect the tiny task-related changes, but also when subtracting the baseline activation, sometimes you get negative activation (Stark & Squire, 2001). As the baseline can to such a large degree influence the activations that are seen, researchers decided to examine the nature and organisation of the brain's resting, or “default”, state (Gusnard & Raichle, 2001; Fox et al., 2005). Knowing which areas are typically active in the resting state, could allow for a more conscious design of experimental and control conditions in neuroimaging. What was found is a particular set of brain areas consistently deactivating when the subject is engaged in some experimental task, with these also consistently coming back online when the subject is not engaged in a task. These brain areas include the posterior cingulate cortex and precuneus, the medial PFC, and the angular gyrus in the parietal lobe (Fox et al., 2005; Shulman et al., 1997).

In 2005, Fox et al. investigated these two networks by calculating correlations in BOLD time course between six seed regions previously known to be important nodes in these networks, and all other voxels. This was done on images taken of three different resting states.

Fox et al.'s (2005) work confirmed that these networks – the DAN and the default mode network (DMN) – acted as networks also in the absence of any task. That is, their activity within network was correlated, and between network their activity was anticorrelated.

The DMN has been associated with daydreaming (Kucyi & Davis, 2014), but this does not mean that it has no productive function. The network has been found to activate when subjects are asked to think about their past, their future, or when taking someone else's perspective, such as when reading a story (Spreng, 2012). Importantly, the DMN has been found to activate together with prefrontal control structures when performing a task that both involved self-reflection and goal-directed cognition (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). This was a task where the subject had to create a plan to reach some personal goal they had, and to account for obstacles that they might face on the way.

Executive Functions Broken Down

Miyake and Friedman (2012) applied factor analysis to several different tests of executive function to try to overcome the problem of «task-impurity», which refers to how in every task meant to test executive function, the score additionally reflects non-executive abilities particular to the concrete form of the task. An example of such non-executive abilities could be colour processing in the Stroop Test. They did this to look for the essential components of these elusive constructs. The main constructs they were interested in were updating, shifting and inhibition. A certain amount of variance was shared among all three, which was termed “Common EF”, and after accounting for this, inhibition contributed no further explanation value, so this was dropped as a separate factor. They also found that the factors “Common EF” and “Shifting-specific” were anticorrelated in certain situations (Miyake & Friedman, 2012). Working memory is an indispensable executive function, which in Miyake and Friedman's (2012) system would cover at least the “Updating-specific” factor,

including the ability to store items across a delay, add new items or otherwise change the items held. “Shifting-specific” seems to cover the ability to rapidly switch between tasks, or set-shifting, but does not fill the requirements of a more comprehensive definition of ‘cognitive flexibility’. This last construct would probably include all three of Miyake and Friedman’s (2012) factors. What’s interesting is that the last factor, “Inhibition”, was absorbed by “Common EF”. This means that all tests of executive function require the ability to inhibit responses. As mentioned previously, to inhibit a prepotent response, there needs to be represented in a person’s mind both a prepotent response, an alternative response, and the ability to override one in favour of the other. In addition to this, two other abilities explain performance on tests of executive function, according to Miyake and Friedman (2012). One, the ability to temporarily store and update the contents of working memory, and two, the ability to rapidly switch between tasks. Being able to concentrate and deliberately control one’s attention could be supported by the same process underlying inhibiting prepotent responses, which means that control of attention and self-control belong to “Common EF”. Allowing one’s attention to wander, then, or allowing new thoughts in to the current mindset, could be partially explained by the “Shifting-specific” factor. “Updating-specific” probably maps pretty cleanly onto the general usage of the term working memory, except maybe for “monitoring”.

The development of tests of executive functions is an important endeavour. These tests are central to both the assessment of clinical therapies and basic research into the neural underpinnings of executive functions. Tests of executive function may not be testing executive functions directly, yet they are presently the best alternative there is. Though there are physiological measures able to some degree to predict executive functioning, such as event related potentials (ERP), the relation between specific ERPs and behavioural function is not always clear (Downes, Bathelt, & De Haan, 2017). The third option is various forms of

behavioural observation, which might hold more ecological validity than formal tests, but are costly to perform. One formal test of executive function is the WCST, which will be discussed next.

The Wisconsin Card Sorting Test

The WCST was presented by Grant and Berg in 1948. In the article from 1948, Grant and Berg used the WCST to investigate the relationship between reinforcement and set-shifting, reinforcement meaning how many correct responses the subject gave before the sorting rule was changed. They found that an increased amount of reinforcing trials did not make it harder for the subject to change the sorting rule when they were told their answer was no longer correct (Grant & Berg, 1948). In the original WCST four stimulus cards were presented to the subject, which had either circles, triangles, crosses or stars, in either a blue, green, yellow or red colour, on them. The number of symbols on each card varied between one to four. The subject was then handed 64 response cards and asked to place them under the stimulus cards according to a rule only known to the investigator – the investigator gave feedback on whether the sorting was right or wrong. When the rule changed after a number of correct sortings, the subject would have to induce that the rule was changed based on no other message than the “wrong”-feedback.

The subject undergoing the WCST has to perform several different mental operations. Initially, the to-be-sorted card must be looked at so that its features, or sorting criteria, can be clearly perceived. These then must be compared to the features available among the target cards. For the very first card, one of the cards has to be picked at random, while for the following cards, the gathered evidence has to be remembered and leveraged for choosing optimally. If the card is sorted according to the wrong rule, this has to be noted, and then it should exclude one possibility for the next round. If the card is sorted according to the right

rule, this rule should be remembered, and attention should be allocated to the perceptual feature that is the rule. That is, the subject should scan the cards for a certain colour, shape, or number (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005; Petersen, Corbetta, Miezin, & Shulman, 1994). Stated briefly, the WCST challenges working memory, the control of attention, cognitive flexibility, and logical deduction.

Milner (1963) later adapted the WCST to her study, where she compared the performance on the test of patients with different brain lesions as a result of operations performed to relieve the patient of epileptic seizures. She concluded that the test was specifically sensitive to lesions in the dorsolateral PFC, and that damage to the posterior regions had a lesser impact on performance on the sorting test. Although this view about the test has been common for many decades, conflicting evidence was provided by Teuber, Battersby, and Bender already in 1951. They had administered the test to wounded soldiers, and their results showed that the soldiers that performed the worst were those with parieto-occipital lesions, and not frontal lesions. Anderson, Damasio, Jones, and Tranel (1991) investigated this disparity more closely, and concluded that though the test was somewhat sensitive to frontal lesions, it was not sufficiently specific to be used as a sole indicator of the presence or absence of frontal lesions.

It would seem, then, that there isn't a dedicated "card sorting centre" in the brain. Lesion studies report effects on performance on the WCST by damage in a number of foci, including the dorsolateral PFC (Milner, 1963; Stuss et al. 2000), the medial PFC (Drewe, 1974), the temporal lobes (Giovagnoli, 2001), the hippocampus (Igarashi et al., 2002), and even the cerebellum (Mukhopadhyay et al., 2008). Neuroimaging studies have been no less ambiguous, with most of them reporting task related metabolic increases in a distributed network of brain areas (Nyhus & Barceló, 2009). In a field made up of complex cognitive functions where there is rarely a simple relation between construct, behavioural measure, and

neural substrate, it would seem that the WCST manages to stand out as involving a more complex set of constructs.

In addition to the unclear relationship between WCST performance and underlying cognitive abilities, and the unclear relationship between these cognitive abilities and their underlying neural structures, there seems also to be ambiguities in the scoring of the WCST. Heaton (1981) published a formalised manual for the administration, scoring and interpretation of the results. The rules included here were that the number of key cards should be four and the number of cards in the response deck should be 128. The sorting rule should change after ten consecutive correct matches. The performance should be measured using sixteen different scales. Many researchers report divergence from these rules (Nyhus & Barceló, 2009; Mountain & Snow, 1993), however, and the scoring system in particular is often simplified. Bowden et al. (1998) investigated the reliability and internal validity of the WCST. They concluded that the different scores all load onto one factor, and that the reliability of the test was so low that clinicians ought not to use it until this had improved.

The variability in the way the WCST is administered makes comparing results from different studies less convenient. The involvement of a complex set of cognitive functions and brain areas in solving the tasks makes drawing conclusions from test performance complicated. Despite these issues, the test continues to be popular. A meta-analysis done in 2003 by Demakis found that the test is indeed sensitive to frontal damage compared to damage in other parts of the brain. Stuss et al. (2000) compared WCST-performance among persons with focal lesions in frontal and non-frontal brain areas, while excluding persons with language comprehension problems and/or detectable neglect. They found that the patients with damage in the frontal areas were significantly impaired, mainly due to perseverative errors and set loss errors.

Persons with frontal lesions are not the only ones with dysexecutive symptoms. Below follows a discussion of the many ways dopamine drives executive functions in light of several conditions characterised by both dopamine dysregulation and dysexecutive symptoms.

Dopamine and Executive Functions

Many patient groups are known to have problems with executive functions, including persons with schizophrenia (Orellana & Slachevsky, 2013), ADHD (Martel, Nikolas, & Nigg, 2007), addiction (Verdejo-García, Bechara, Recknor, & Pérez-García, 2006), and persons with Parkinson's disease. People with Parkinson's disease are moderately to severely impaired on the WCST (Lange, Brückner, Knebel, Seer, & Kopp, 2018). The catecholamine dopamine has been implicated in many conditions in which executive functions also are said to be disrupted. These include ADHD (Volkow et al., 2009), substance abuse (Berridge & Robinson, 2016), Parkinson's disease (Fahn, 2008), and schizophrenia (Howes, McCutcheon, & Stone, 2015). Although dopamine can have many different effects, depending among other things upon concentration, receptor density or which structures are involved (Cools & D'Esposito, 2011; Durstewitz & Seamans, 2008), it seems worthwhile to explore what possible commonalities exist, given that a single molecule can have such wide ranging effects.

Dopamine is distributed through three pathways in the brain; 1) mesolimbic, from the ventral tegmental area to the nucleus accumbens 2) mesocortical, from the ventral tegmental area to the frontal cortex 3) nigrostriatal, from the substantia nigra to the striatum (Wickens, 2009). The mesolimbic pathway is associated with reward and motivation, and is implicated in addiction (Berridge & Robinson, 2016). The nigrostriatal is associated with motor action selection, and is implicated in Parkinson's disease (Fahn, 2008). The mesocortical pathway is less understood, but it has been hypothesised that dysfunction in this pathway is what's

causing the cognitive and negative symptoms of schizophrenia, and so would be involved in executive and social functioning (Weinstein et al., 2017).

Dopamine and Motivation. One of the earliest discoveries about dopamine's functions was its role in reward and reinforcement. It should be noted, however, that dopamine wasn't yet found to be a neurotransmitter when the first discoveries were made (Carlsson, Lindqvist, Magnusson, & Waldeck, 1958). It was found that rats were willing to work very hard for the reward of having their mesolimbic pathway electrically stimulated (Olds & Milner, 1954), which prompted researchers to conclude that this molecule mediated feelings of pleasure. In the same vein, rats were also found to be motivated to acquire dopaminergic drugs (Pickens & Harris, 1968). The idea that dopamine equated to pleasure was modified later, when "wanting" and "liking" were found to be dissociable (Berridge, Venier, & Robinson, 1989). Dopamine in the mesolimbic pathway is now mostly thought to underlie motivation (Berridge & Robinson, 2016), although the experience of feeling motivated might still be enjoyable in and of itself (Healy, 1989). In a review by Robbins and Everitt (1992), two different roles for dopamine are reported in the same brain area, the striatum. Blocking dopamine action in the ventral striatum, either through dopamine antagonists or through lesions, leads to a state very much like avolition, where the rats don't seek out rewards, like food or mates. Blocking dopamine action in the dorsal striatum, on the other hand, seems to abolish the actual consuming of rewards once they are acquired. These effects have been doubly dissociated, with rats working for food, but not eating it, and rats not working for food, but eating it if placed in front of them (Robbins & Everitt, 1992). Even here, we can see that two separable functions, seeking and consuming, still have one thing in common, that they both are directed towards rewards. Salamone, Cousins, and Snyder (1997) state that "rewards" is not exactly what dopamine is signalling in the mesolimbic pathway,

but rather motivational salience in general. This means that dopamine supplies the incentive not only to approach pleasurable stimuli, but also the incentive to avoid aversive ones.

The dorsal striatum, which is the target of the nigrostriatal pathway, has since been found to underlie associative learning, habit formation, and motor sequence gating (Yin & Knowlton, 2006). Using Antzoulatos and Miller's (2011; 2014) experiments on category learning in macaques as an example, one might imagine that the striatum was learning what to do about some pictures to get treats. Perhaps in the beginning it was mapping to each individual picture a response that would be good. As more and more new pictures were shown to it, the striatum started feeding the PFC all these individual truths, and then the PFC started extracting the similarities among all the "look left"-pictures and all the "look-right"-pictures, until, in return, it could teach the striatum to ignore the irrelevant differences making the pictures unique, and instead only focus on whatever features made the categories what they were, and then simply respond as if there were only two pictures. One important thing to point out here is that the PFC was only able to extrapolate the categories from the individual pictures because there was some commonalities to extrapolate.

Executive Functioning and Dopamine. Dopamine was also found to play a role in executive functions when rhesus monkeys with a regional depletion of dopamine were impaired in a delay task (Brozoski, Brown, Rosvold, & Goldman, 1979). Cools and D'Esposito (2011) propose that dopamine is central to working memory function, but that the optimal concentrations lie in the middle of an inverted U-shaped curve. Because of this, they suggest that the baseline levels of dopamine should be taken into account when investigating the effects of dopaminergic medication on cognitive abilities. Another proposal in Cools and D'Esposito (2011) was that dopamine has opposing effects on the PFC versus the striatum, partly motivated by the difference in distribution of D1 versus D2 receptors. Durstewitz and Seamans (2008) also proposed different effects of dopamine on cognition, depending on the

balance between D1 and D2 binding. They didn't connect this difference to brain structure, though, and instead suggested that there were certain dopamine concentrations more amenable to D1-binding and others more amenable to D2-binding.

In a study by Puig and Miller (2014), it was found that blocking D2-receptors in the monkey lateral PFC impaired associative learning, cognitive flexibility (operationalised as number of perseverative errors), and motivation. In 2012, Puig and Miller had shown that blocking D1-receptors impaired associative learning and cognitive flexibility. There was, however, an imbalanced distribution of reduction in associative learning and flexibility, where D1-blocking had a stronger effect on learning, while D2-blocking had a stronger effect on flexibility. Puig and Miller (2014) suggested that this could indicate that D1 activation is involved in maintaining a representation, while D2 activation “destabilizes PFC network states favoring the exploration of new strategies” (Puig & Miller, 2014, p. 2985).

Dopamine has been shown to influence task performance through a modulation of the DMN (Nagano-Saito, Liu, Doyon, & Dagher, 2009; Dang et al., 2012). In Nagano-Saito and colleagues' (2009) study, administration of a dopamine receptor agonist made reductions in DMN activity sensitive to task complexity, so that increasing task complexity resulted in larger reductions in DMN activity. In Dang and colleagues' (2012) study, higher dopamine synthesis capacity in the striatum was correlated with lower performance in shifting among object features and a weaker reduction of DMN activity. Whether the study by Dang et al. (2012) shows that dopamine is beneficial or detrimental to task performance is equivocal, as a higher synthesis capacity is only one aspect of dopamine transmission (Berry et al., 2018; Nour, McCutcheon, & Howes, 2018).

Methylphenidate and dextroamphetamine work by enhancing dopamine action – these substances are both prescribed to persons who suffer from ADHD (Seeman & Madras, 2002), a condition characterised by impulsivity, hyperactivity and inattentiveness (American

Psychiatric Association, 2013). Given the dopaminergic medications' ability to improve these symptoms, it would seem dopamine somehow aids in concentration and willpower. Whether it does this by increasing the motivational salience of tasks or whether it does it by strengthening control processes' ability to control, is not known. One group of people who do not benefit from dopamine agonists, are those suffering from schizophrenia.

Dopamine – The Point to Cognition. Dopamine plays a central role in motivating behaviour, i.e. it drives a person's goals. It drives the feeling of importance that behaviourally relevant activities have. It also is central to a very basic form of learning, where whatever one learns, the dopaminergic "value" of it is also automatically encoded. Though not everything one learns is necessarily associated with a dopaminergic valence (Tolman, 1948), things that are interesting or that feel important (i.e. things that have been associated with reinforcement) are learned faster and better (Rescorla & Wagner, 1972; Treviño, 2016). For these reasons, not only is the fast, concrete learning of the basal ganglia enhanced by the right concentrations of dopamine, but also the PFC, when trying to maintain something in working memory, or staying focused on a task, or trying to inhibit an inappropriate response in favour of the more effortful one, is afforded some extra horsepower by dopamine. The strange thing is that it is also dopamine that creates the obstacles for the PFC to do its job. When trying to stay focused on a task, it is the salience of distracting stimuli that must be overcome, and it is dopamine that imbued those stimuli with salience. Normally, the salience of things arises organically. Some fundamental things like food or people are salient because they are inherently relevant to one's existence, while other things like a well-equipped kitchen or a telephone become salient through their association with food and people, respectively. In psychosis, however, salience seems to be transferred to stimuli in a chaotic manner (Kapur, 2003).

Dopamine in Schizophrenia. The final function of dopamine to be discussed here is not really a function, but rather a dysfunction. Psychosis is defined as a loss of connection with external reality. Symptoms include delusions, hallucinations, and disordered thought and speech (American Psychiatric Association, 2013). Psychosis is probably the most recognisable feature of schizophrenia, an illness that is also characterised by disorganised speech, disorganised behaviour, and negative symptoms (American Psychiatric Association, 2013). Most pharmacological treatment options for psychosis since the 1950s have been antagonistic to dopamine in some way (Howes et al., 2015). This made researchers think that dopamine was central to the pathophysiology of schizophrenia (Baumeister & Francis, 2002). Although the causes of the condition are not fully understood, most of the theories surrounding schizophrenia assume dopamine dysregulation at some point in the causal chain (Corcoran, Mujica-Parodi, Yale, Leitman, & Malaspina, 2002; Fletcher & Frith, 2009; Howes et al., 2015; Javitt, 2010; Kapur, 2003). Instead of trying to understand the underlying cause of schizophrenia, this section will focus on attempts at explaining the role of dopamine in schizophrenia and psychosis.

One theory postulates that psychosis is caused by excessive amounts of dopamine in the striatum, and is called the “aberrant salience hypothesis” (Kapur, 2003). Kapur (2003) illustrates how excess dopamine imbues normally inconsequential thoughts and stimuli with an increased sense of importance, or motivational salience. The idea is then that this abrupt sense of importance invites the person with schizophrenia to supply fanciful accounts explaining the warped motivational salience of thoughts and environment. Dopamine antagonists, then, relaxes this salience and creates some «motivational room» where the delusions are allowed to subside and resolve. Kapur (2003) underscores, however, that the antipsychotics do not directly dissolve the delusions as if by a supplement of pharmacological clarity, they only reduce their salience which creates space for alternative thoughts to emerge.

If the delusions are not addressed cognitively during pharmacological treatment, de novo psychosis post-treatment often revolves around the same subjects as the original psychosis.

There have been reports that prognosis worsens with time passed between the first episode of psychosis and treatment (Harrison et al., 2001). Seen within the parameters of Kapur's (2003) theory, this might be reflecting a process of learning. Recall that the striatum recognises and learns the association between concrete phenomena and their dopaminergic value. When in a psychotic state, the dopaminergic value of phenomena is aberrant, according to Kapur (2003). The longer it takes before an individual receives treatment, the more time the striatum has to learn all these aberrant associations. This would contribute to consolidating a very different and fundamentally disordered experience of the world. Assuming that the PFC depends on the striatum for reliable and coherent streams of experiences to be able to draw out the essences and generalise, a protracted psychosis could disrupt the very basis of abstract thought. This would make it hard to recover via cognitive behavioural therapy, for instance. In addition, relating to other people would become progressively more difficult, as communication relies on an enormous amount of shared assumptions about the world and about what's important in life.

A possible trajectory from an untreated psychosis towards worsening cognitive symptoms was outlined above. However, there have also been reports stating that the cognitive symptoms of schizophrenia precede the first episode of psychosis (Caspi et al., 2003). Findings like these make it difficult to determine the direction of causality between psychosis and cognitive symptoms. It is still striking that all of the symptoms of schizophrenia can be predicted from various abnormalities in dopamine concentration (Durstewitz & Seamans, 2008).

People with schizophrenia do not only suffer from psychotic symptoms. The disorder is also characterized by negative symptoms which refer to an impairment in normal

functioning. The negative symptoms include symptoms related to motivation – avolition, asociality and anhedonia – and affect that is blunted, and alogia (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). In addition, people with schizophrenia also show deficits in executive functions, such as working memory (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005) and attention (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Everett, Lavoie, Gagnon, and Gosselin (2001) report from an experiment comparing patients with schizophrenia with controls in the WCST, that the patients with schizophrenia made significantly more errors and completed fewer categories. They report that the patients with schizophrenia did more perseverative errors, but they also report that considerably more trials were needed for them to complete the first category, so their impairment wasn't necessarily specific to perseveration.

Using Miyake and Friedman's (2012) system, what seems to be the issue in the schizophrenic brain is an overabundance of "Shifting", where anything can seem important and grab attention. Whether this is in a direct causal relationship with an impoverished "Common EF" (inhibition), or if these two features develop in parallel is not clear from the research discussed here, though Miyake and Friedman (2012) did point out that these two factors were anticorrelated in certain situations. It seems likely, though, that if everything and anything can seem important, then this would have an antagonistic relation to the ability to deliberately choose one response or thought over another. One could easily conceive how this imbalance between shifting and inhibition could lead to avolition. If avolition is defined by the lack of motivation to achieve goals, and the way this motivation is represented by the brain looks like what Holroyd and Yeung (2012) described, with the ACC setting up a hierarchy of salience, basically, then this hierarchy would be impossible to construct if anything can seem equally important. This would quite effectively disrupt any long-term plans.

Kapur (2003) proposes that aberrant salience explains both hallucinations, delusions, and disordered thought and speech. These symptoms by themselves seem likely to explain the negative and cognitive symptoms of schizophrenia, but the way antipsychotics reduce the positive symptoms while not impacting the negative ones (Remington et al., 2016), challenges this very intuitive understanding.

Schizophrenia remains a mysterious condition with several observations that are difficult to integrate into one coherent, aetiological theory (Harper, Towers-Evans, & MacCabe, 2015). Although the hallucinations and delusions may be the most recognisable symptoms, it is actually the cognitive symptoms that have the most profound impact on the patient's life (Green, Kern, & Heaton, 2004; Green, 2006; Bliksted, Videbeck, Fagerlund, & Frith, 2017). In order to study these, and eventually develop better treatment options, good neuropsychological tests are needed. Such tests should be challenging enough to distinguish between healthy and patients, while also being sufficiently specific to distinguish between different functions. Therefore, it is relevant to uncover exactly which neural structures are being engaged by the tests already created. One attempt at this will be described below.

Experimental Design

The aim of the study was to develop an auditory adaptation of the WCST, which would allow for testing of the visually impaired. The second aim was to explore the commonality between the auditory and visual variants of the test, investigating the neural substrates of performing the WCST when maintenance of information in short-term memory was controlled for. In this study, four different versions of the WCST were used. These could be categorised by modality and difficulty level. In the visual modality, there was one original WCST, called "Uninstructed Visual", and one where the subject was informed of the sorting rule of the WCST, called "Instructed Visual". The pattern was the same for the auditory

modality. The translation from the visual to the auditory modality was done as follows. Instead of decorated cards as stimuli, the subjects were to perform the sorting tasks on speech recordings as stimuli. The stimuli varied along three dimensions – voice actor, syllable, and number of repetitions. The design and execution of the experiment was done by Professor Karsten Specht, while the processing and analysis of the data were performed by the author.

The following were the hypotheses of the study:

- 1) Comparing the visual task with the auditory task will only show differences in sensory cortex.
- 2) Comparing the uninstructed sorting task with the instructed sorting task will show activation more specifically related to executive functions, such as the dorsolateral prefrontal cortex, anterior cingulate and parietal cortex.
- 3) Comparing average activation across all tasks with rest will show more activation related to working memory, possibly in posterior cortex.

Methods

Subjects

16 healthy, male subjects between the ages of 19 and 29 participated in the study. They were all right handed as determined by the Edinburgh Inventory (Oldfield, 1971), and were naïve to the WCST. Informed consent was acquired from every subject, and the regional ethics committee approved the study.

Materials

The Edinburgh Inventory. The Edinburgh Inventory (Oldfield, 1971) was administered to determine the handedness of the subjects. This inventory includes 15 items asking for the subject's preferred hand to use in different circumstances.

3T GE-Signa MRI Scanner. When performing fMRI the BOLD signal is utilized. This is an MR-signal that occurs as a result of how the magnetic properties of deoxygenated and oxygenated blood differ (Lindquist, 2008). When haemoglobin, which is a metalloprotein in the red blood cells, is oxygenated it is diamagnetic, which means that the magnetic force repels it. When the oxygen in the haemoglobin is released, it is paramagnetic, which means that the magnetic force attracts it. Since there is no oxygen stored inside the neurons, more active neurons require more blood. The blood supply in one area is depleted of its oxygen faster, when groups of neurons in the area become more active. This leads to a reaction in the blood vessels, and they expand. This generates an increased blood flow, and as a result more oxygenated blood is sent to the activated group of neurons, which is named the hemodynamic response function (HRF) (Lindquist, 2008). The whole process is registered by the MR-scanner as a slight reduction in signal right after an area becomes more active, swiftly followed by a rising signal strength as the balance between oxygenated and deoxygenated blood shifts. Signal strength peaks in most cases at 4-6 seconds after the neurons start firing. However, the BOLD-signal can be difficult to detect. The brain is always active, and the activity that is evoked when the subject is performing experimental tasks, is only a tiny fraction of the overall activity of the brain. To solve this issue, the task or behaviour that is to be mapped to a brain area often is repeated multiple times to get an increased signal-to-noise ratio. The activation of the target behaviour is recorded along with repeated blocks of a control condition. The activation pattern of the control condition is then subtracted from the activation of the experimental condition, and it is assumed that the neural activity that remains after this subtraction is the activity related to the behaviour of interest particularly. This procedure is called cognitive subtraction. A scanner trigger was used to allow for coordination between the image acquisition and stimulus presentations.

Stimuli Presentation. The auditory stimuli were presented through headphones from Nordic Neuro Lab (NNL), which also allowed for two-way communication between subject and staff. At the same time the headphones shielded the subjects from high noise levels coming from the scanner. The visual stimuli and instructions were displayed on an LCD screen, also from NNL. The subjects submitted their responses by pressing the buttons on an input unit, also from NNL.

Stimuli Production. Audio recording and editing was performed with the computer software Adobe Audition 2.0, while the four versions of the WCST were created together with their presentation order in the computer software E-prime (version 1.1, Psychology Software Tools Inc.). E-prime allows for synchronisation between the scanner and the presentation of stimuli, through the use of triggers and markers.

SPM12. Statistical parametric mapping (SPM12) is a set of statistical procedures developed by Friston et al. (1994) to analyse neuroimaging data in an experimental setting, i.e. to test specific hypotheses. It involves assuming parametric statistical models at each voxel, which when tested according to whichever hypothesis one has, results in a map showing all voxels that do or do not conform to the hypothesised pattern of activation. A software tool designed to implement these procedures was developed by the Wellcome Department of Imaging Neuroscience.

MRICroGL. Figures showing the activations were made by importing contrast maps from SPM12 into MRICroGL (v1.0.20180623) This software then projected the activations on a 3D-rendered model of the brain. MRICroGL was developed by the McCausland Center of University of South Carolina.

Design

The experimental design included two factors with two levels each. The factors were labelled “Difficulty” and “Modality”. “Difficulty” had the levels “Instructed” and “Uninstructed”, while “Modality” had the levels “Visual” and “Auditory”. Altogether, this yielded four different tasks that the subjects were presented with. There were two runs per subject, one for each modality. Within each run, blocks of the instructed and the uninstructed sorting task were presented in an intermingled fashion. Each task block lasted 60 seconds, with 20 second periods of no task in between. In total, there were 24 task blocks, and 12 per run.

Procedure

The paradigm was built in E-prime (version 1.1). Prior to running the experiment, the paradigm was tested in a pilot study done on five subjects.

Uninstructed Tasks. Two experimental tasks were used. The visual sorting task was adapted from the original WCST. In this task, two cards with different symbols, in different colours and numbers, were shown following each other. The symbols were either circles, squares, stars or triangles; the colours of the symbols were red, blue, green and yellow. The number of symbols on each card ranged between one to four. The subjects were to deduce what the mutual feature of the presented cards was. To figure this out they would have to try different sorting rules, and succeed or fail. The E-Prime program communicated through a response screen whether their answer was right, and the subjects had to make changes in their sorting rule based on this feedback. When a subject found the right sorting rule, he or she was to follow this rule for the following trials. However, this rule changed at each new task block in the experiment. When the feedback on the response screen communicated that their choice

was now incorrect, the subject would have to adjust their choice of sorting rule and find the new correct rule.

The auditory uninstructed sorting task was an original adaptation of the WCST created for the present study, named the Auditory Sorting Task (AST). In the AST, the stimuli to be sorted are speech recordings, which vary along three dimensions: syllable (ba, da, pa, ta), voice (four different actors), and number of repetitions (one to four). As only the stimuli are different between the auditory and the visual task, the AST also follows the delayed matching procedure described above. The recordings were captured in Adobe Audition 2.0, inside of an echo reduced chamber. Four different male actors read aloud from a list of syllables. During the recording, the actors read each syllable several times from a list, and the order of the syllables was varied, so that there were no systematic differences in intonation between the syllables. The recordings that sounded most neutral and homogeneous in intonation were chosen as stimuli for the AST.

Instructed Tasks. The instructed tasks mirror the two tasks described above, except for the inclusion of a message ahead of every task block informing the subject of which stimulus feature to attend to. As this obviates the need to test one sorting rule while maintaining another rule as a possibility, it was thought that this would be less taxing on the executive system. If used as a high level control condition, it was hypothesised that this would remove activation related to simple storage of short-term information – as this would be functions common to both tasks. What would then be left was thought to be activation related to executive functions like set shifting.

Data Acquisition. Each subject was in the scanner for two runs, once for the visual tasks and once for the auditory tasks. The experimental conditions were introduced to the subjects prior to entering the scanner, and so they were aware of the variety of sorting dimensions. However, they were not explicitly told about how the rules would change. One

half of the subjects began with the visual task and the other half began with the auditory task, in order to control for learning effects. The subjects were instructed to respond using remote controls as to whether two consecutively presented stimuli were the same or not the same along the presently applicable dimension. One half of the subjects responded “yes” with their right hand while responding “no” with their left hand, and this configuration was reversed for the other half of the subjects. Each block in both runs was preceded by a task instruction presented on a screen. The visual tasks were shown on the same screen, while the auditory tasks were delivered through headphones.

The data were collected with a 3T GE-Signa MRI scanner. A structural T1-weighted image was taken of every subject. The functional images were taken with a T2*-weighting in combination with echo-planar imaging. The presentation of stimuli was synchronised with the acquisition of the functional images through triggers sent between the scanner and the computer running E-prime. 360 whole-brain volumes were gathered in each run. The repetition time (TR) was 2.5 seconds, and gaps of one second were left in between the TRs to reduce noise when presenting the auditory stimuli. The acquisition time (TA) was 1.5 seconds. A non-cubic voxel size of $1.72 \times 1.72 \times 4.40$ was used within a 64×64 matrix.

Preprocessing and Statistical Analyses

Preprocessing and analyses were done using the SPM12 software package (Wellcome Centre for Human Neuroimaging, 2014) within MATLAB 9.4 (The MathWorks Inc., 2018). The time-series was realigned to the first image, and then unwarped to compensate for deformations around air-tissue interfaces. These were then normalised to fit the coordinate system of Montreal Neurological Institute, and re-sampled to a voxel size of 2 mm^3 . Finally, the images were smoothed with a Gaussian kernel of FWHM 8 mm to satisfy the assumptions of subsequent statistical analyses.

The two sessions (auditory and visual) of each participant were modelled separately in a blocked design. The canonical HRF was used with no derivatives. Responses were not included in the model, but realignment parameters were. The data were filtered with a high-pass filter of 450 seconds. Contrasts were estimated for the main effects of the experimental condition and the instructed condition, as well as the latter's effect subtracted from the former's effect.

Looking at the group effects, a within-subject factorial analysis of variance with Modality and Difficulty being the factors was performed. These had two levels each; Visual and Auditory, and Instructed and Uninstructed. The contrasts of interest were the main effects of the factors, unique effects of Uninstructed versus Instructed, and positive effect of condition (average vs. baseline). A conjunction analysis testing against the global null hypothesis was performed on the contrast Uninstructed minus Instructed, because of suspected undue influence of Modality-specific variance. A threshold of $P < 0.05$ (FWE-corrected) was applied to correct for multiple comparisons. Extent threshold was 15.

Short Explanations of Preprocessing and Analysis Procedures.

Slice Time Correction. The images resulting from an fMRI-scan are of vertical and horizontal slices of the brain, and these images can't be registered from the whole brain simultaneously. This means that between an image of a slice of the bottom of the brain, and an image of a slice of the top of the brain, there might be a delay. This needs to be corrected to perform analyses of the resulting images. To correct this one can use calculations to see the resulting images as if they were registered simultaneously. One way to do this is by temporal interpolation, which involves estimating the BOLD signal from what it was just before or just after. Another way is through something called phase shift, which involves moving the whole time series so that it aligns with a reference slice, for example the middle slice.

Realignment and Unwarping. When registering images in an MR-machine, different sources can produce noise that affects the results. Head movement during fMRI is a noise-source that can have a significant impact on the results. Due to head movement, the voxels that cover the brain tissue in one area at one point in time could be covering a different area of the brain at another point in time. To perform analyses of the brain images one has to correct eventual head movements' impact. This problem is solved by realigning all the obtained images of one individual brain, to the first registered image of the current individual. This is done by rotating the image, translation of the image, scaling, and shearing. Nonlinear transformations, which in this case are called unwarping, are also needed in some cases, because of the magnetic field being warped by air-tissue interfaces.

Co-registration. The fMRI images are also warped to fit the dimensions of a structural image, so that the structural image can be used as a background for the activations. This can aid in determining the location of ambiguous activations in single subjects.

Normalization. Every individual brain is built so that they are all unique. This leads to voxels not representing the same brain tissue areas when performing fMRI on different brains. This represents a problem when working with data obtained from several different subjects, and to solve this, the images of every brain has to be warped so that they fit a coordinate system that is common for all the imaged brains. The Montreal Neurological Institute (MNI) has created one such coordinate system, called the MNI space. Several normal MR brain images were combined to create this system (Collins, Neelin, Peters & Evans, 1994).

Spatial Filtering. Spatial filtering, or spatial smoothing, is the final step in the preprocessing of the images. The process of normalising several brains to a single mould sometimes leaves residual differences and abrupt borders. These have to be smoothed out in order to satisfy the distributional assumptions of later statistical analyses. Even though this reduces the images' spatial resolution, it may also increase the signal-to-noise ratio.

After Preprocessing. When fully preprocessed, the images are ready to be analysed. First, the images are analysed on a subject to subject, and scanning session by scanning session, basis. The first step is to assume a general linear model (GLM) at each individual voxel which describes the variation in signal strength across time in terms of the experimental conditions, known sources of noise and residual error. This model can be expressed as the following equation, $Y=X\beta+\epsilon$. In the present experiment, there were 8 regressors, two for each experimental condition (instructed sorting and uninstructed sorting) and six realignment parameters which controlled for head movement. The experimental conditions were convolved with the HRF, which accommodates a more natural shape in the BOLD curve instead of an abrupt on and off. Since a blocked design was used, there was no need to explore more specific convolutions, as these would not be visible anyway across such timespans. The betas, or regression coefficients, were estimated using the information known to the researcher, such as the onsets of the different experimental blocks and the recorded BOLD signal. Looking for the configuration resulting in the least amount of error, SPM12 calculated the estimated contribution weight of each regressor at each voxel at each timepoint. This resulted in a number of maps equal to the number of regressors, with each map showing the contributions of one regressor for every voxel in the brain. These maps could then be contrasted against each other in different ways, resulting in contrast maps showing for example which voxels activated more to condition A versus condition B. The contrasts in each voxel could then be tested against the null hypothesis, allowing for inferences about causality to be made. Since there were being done tests in numbers proportional to every single voxel in the brain, a strict threshold for statistical significance had to be set, to control for false positives. The two main approaches to correcting for multiple tests are the familywise error rate (FWE) correction and the false discovery rate (FDR) correction. FWE controls the rate of any false positives across the whole set of tests performed, while FDR

controls the ratio of false positives to false negatives, and so FWE is the more stringent of the two. In the present experiment, a version of FWE was used that accounted for the fact that most voxels in the brain are correlated with other voxels to some degree, which means that the number of truly independent tests is lower than the number of voxels. The FWE-alpha was set to 0.05. When the relevant contrast maps for each scanning session for each subject were acquired, group analysis, or second level GLM, could commence. The contrast maps of interest for each subject were added to a second level GLM which now had a new regressor, namely the variance between subjects. The contrast maps used were simply of which voxels were significantly more active under Uninstructed Sorting compared to baseline, and which voxels were significantly more active under Instructed Sorting compared to baseline. These came in two sets, namely Visual and Auditory. From these, a 2x2 analysis of variance was performed, allowing for detection of main effects of Modality and of Difficulty, as well as interaction effects.

Results

The main effect of Modality was seen only in voxels at auditory and visual cortices. A pair of clusters stretching from the lateral edges of middle and superior temporal gyrus to the posterior insula and central operculum, bilaterally. Another band of activation is seen across the calcarine cortex to the lingual gyrus. See Table 1, and Figure 1.

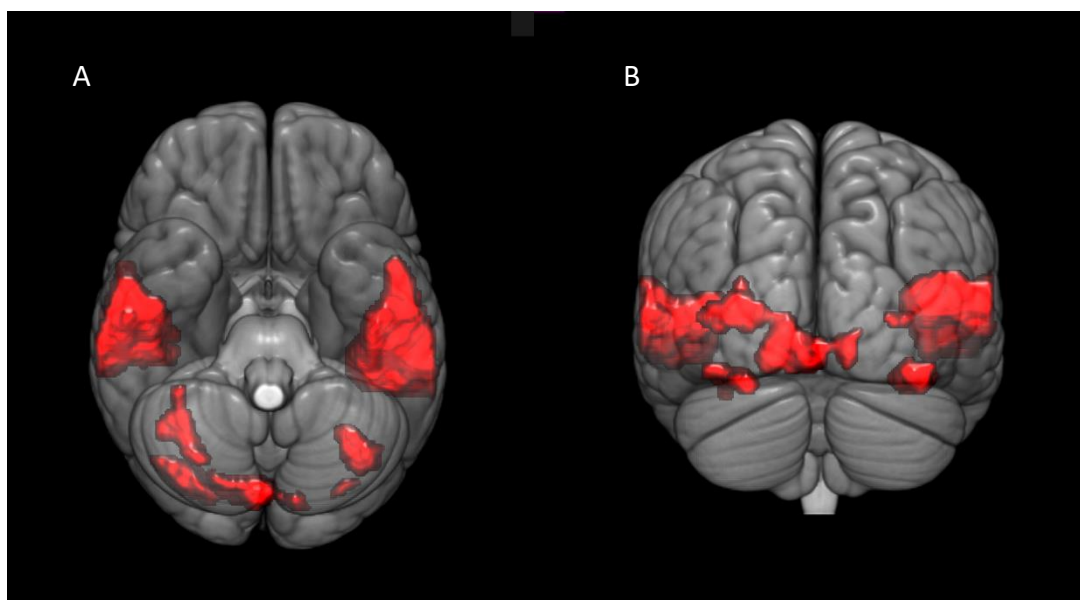


Figure 1. Main effect of Modality. A: Inferior aspect, B: Posterior aspect.

Table 1
Main effect of Modality

Cluster		Voxel			Anatomical location			
p(FWE)	Size	p(FWE)	<i>F</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	Area
0.000	2786	0.000	114.43	7.71	-52	-20	0	Left superior temporal gyrus
0.000	2126	0.000	111.56	7.65	66	-22	0	Right superior temporal gyrus
0.000	843	0.000	60.49	6.24	6	-84	-10	Right lingual gyrus
0.000	247	0.000	58.22	6.15	-36	-70	-18	Left occipital fusiform gyrus
0.000	229	0.003	37.25	5.17	28	-70	-22	Right occipital fusiform gyrus
0.007	27	0.0136	31.37	4.81	-34	-80	4	Left inferior occipital gyrus

The Uninstructed minus the Instructed condition, showed bilateral activation across inferior occipital gyrus and occipital fusiform gyrus, extending ventrally to the cerebellum

and medially to the lingual gyrus. There was also a blotch of activation at the medial center of supplementary motor area (SMA), as well as bilateral activation at precentral gyrus, on the edge of middle frontal gyrus. In addition there was bilateral activation at parietal lobules, supramarginal gyrus and angular gyrus. There was also some activation at the right superior temporal gyrus, and bilateral activation at anterior insula. See Table 2, and Figure 2.

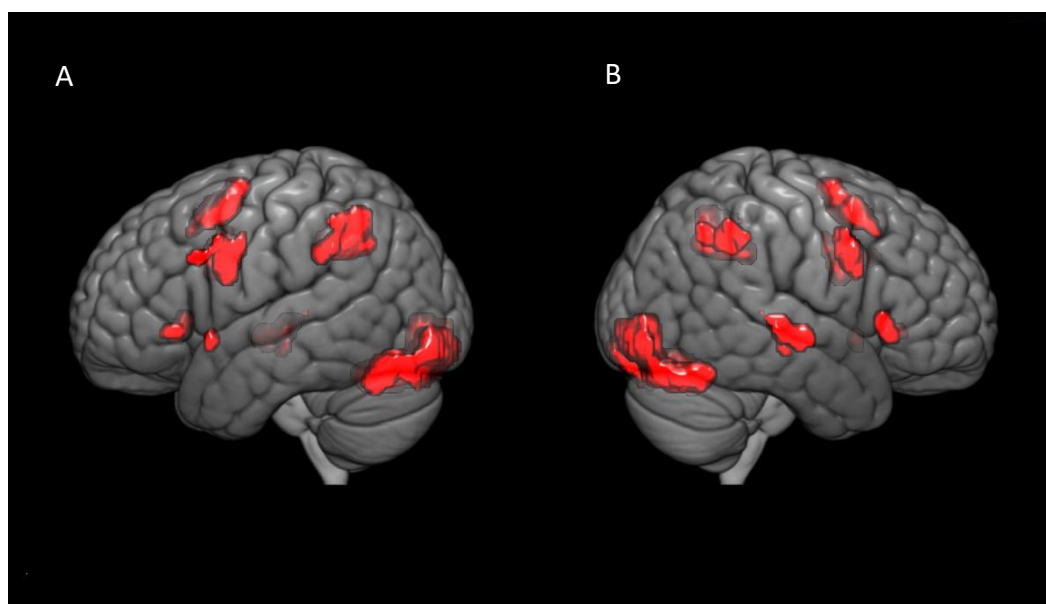


Figure 2. Uninstructed minus Instructed. A: Left aspect, B: Right aspect.

Table 2

Uninstructed minus Instructed

Cluster		Voxel			Anatomical location			Area
p(FWE)	Size	p(FWE)	<i>T</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	
0.000	1372	0.000	9.29	7.15	28	-90	-8	Right occipital fusiform gyrus, right inferior occipital gyrus
0.000	1087	0.000	8.91	6.96	-20	-90	-14	Left occipital fusiform gyrus
0.000	561	0.000	7.69	6.29	-30	-54	42	Left superior parietal lobule
0.000	502	0.000	7.43	6.14	6	10	52	Right supplementary

								motor cortex
0.000	271	0.000	6.95	5.85	42	8	34	Right middle frontal gyrus
0.000	222	0.001	6.29	5.43	60	-24	0	Right superior temporal gyrus
0.000	306	0.001	6.29	5.42	-42	4	28	Left precentral gyrus
0.001	75	0.004	5.81	5.10	34	24	-2	Right anterior insula
0.010	23	0.004	5.78	5.07	-52	10	-8	Left temporal pole
0.006	33	0.005	5.7	5.02	-30	28	-2	Left orbital inferior frontal gyrus
0.000	196	0.006	5.65	4.99	38	-48	38	Right angular gyrus, right superior parietal lobule
0.014	16	0.017	5.31	4.74	48	-22	-10	Right middle temporal gyrus

In comparison, the Instructed minus the Uninstructed condition revealed almost exclusively activation in the precuneus and posterior cingulate cortex. See Table 3, and see Figure 3 for combined map of activations exclusive to Uninstructed and activations exclusive to Instructed.

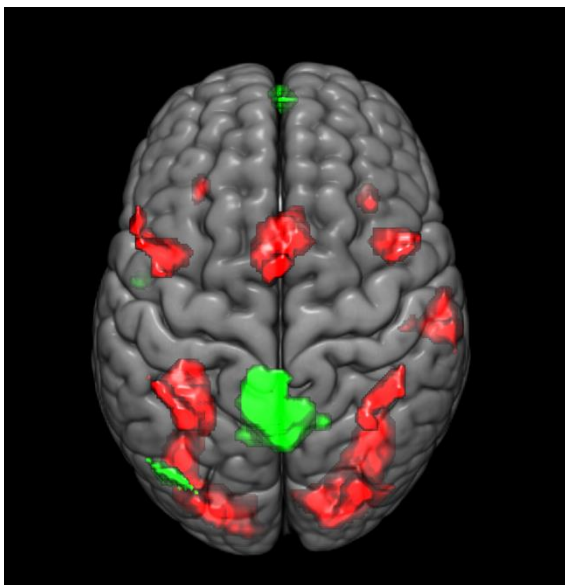


Figure 3. Green: Instructed minus Uninstructed, Red: Uninstructed minus Instructed.

Table 3

Instructed minus Uninstructed

Cluster		Voxel			Anatomical location			
p(FWE)	Size	p(FWE)	<i>T</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	Area
0.000	1105	0.000	7.74	6.32	6	-58	22	Right precuneus
0.001	99	0.000	7.59	6.23	-44	-78	24	Left middle occipital gyrus
0.001	76	0.000	6.60	5.62	0	62	-2	Frontal pole
0.013	17	0.005	5.72	5.04	-54	-8	-26	Left middle temporal gyrus

After applying the conjunction analysis to the Uninstructed minus Instructed contrast, a much cleaner version of the same pattern was seen, with clear activation centres at SMA, and bilaterally at FEF, IPS, and occipital fusiform gyrus. See Table 4 and Figure 4.

Table 4

Conjunction analysis of Uninstructed minus Instructed

Cluster		Voxel			Anatomical location			
p(FWE)	Size	p(FWE)	<i>T</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	Area
0.000	131	0.000	6.09	7.77	28	-92	-10	Right occipital fusiform gyrus
0.000	149	0.000	5.39	7.09	-26	-92	-16	Left occipital fusiform gyrus
0.000	574	0.000	5.24	6.95	-32	-50	40	Left superior parietal lobule
0.000	438	0.000	4.75	6.44	6	10	52	Right supplementary motor cortex
0.000	173	0.001	3.86	5.46	-42	2	30	Left precentral gyrus
0.000	105	0.002	3.77	5.36	44	6	34	Right precentral gyrus, right middle frontal gyrus
0.000	183	0.002	3.69	5.26	34	-54	40	Right angular gyrus, right superior parietal lobule

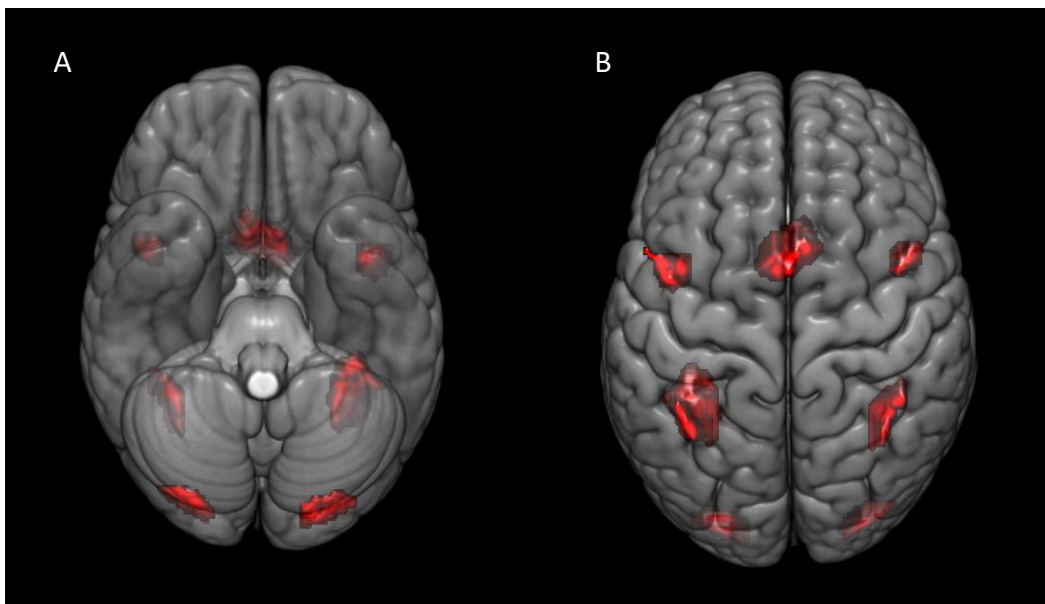


Figure 4. Conjunction analysis of Uninstructed minus Instructed. A: Inferior aspect, B: Superior aspect.

The average positive effect of condition as compared to baseline is shown in Figure 5 and Table 5. When the conditions were not subtracted from each other, activation was visible across the middle and inferior frontal gyri, bilaterally, as well as the ACC.

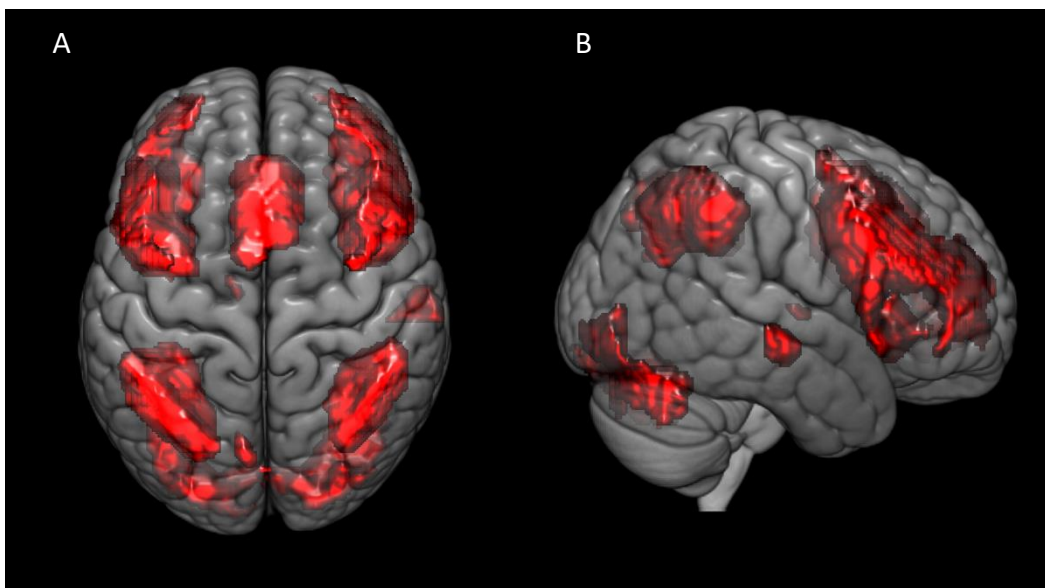


Figure 5. Average positive effect of condition. A: Superior aspect, B: Right aspect.

Table 5
Average positive effect of condition

Cluster		Voxel			Anatomical location			
p(FWE)	Size	p(FWE)	<i>T</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	Area
0.000	2684	0.000	14.08	65535	-36	-56	46	Left angular gyrus
0.000	5104	0.000	12.65	65535	42	8	34	Right middle frontal gyrus
0.000	4521	0.000	12.14	65535	-40	6	30	Left precentral gyrus
0.000	2148	0.000	10.58	7.75	46	-46	46	Right angular gyrus
0.000	1750	0.000	10.45	7.69	-2	20	48	Left supplementary motor cortex
0.000	3238	0.000	9.17	7.09	28	-90	-8	Right occipital fusiform gyrus
0.002	58	0.000	6.81	5.76	-6	-76	40	Left precuneus
0.000	201	0.000	6.57	5.61	62	-16	-12	Right middle temporal gyrus
0.012	20	0.023	5.21	4.67	-12	-10	4	Left thalamus

Discussion

The goals of this study were to develop an auditory adaptation of the WCST, and to investigate the commonality between the auditory and visual variants of the test. It was hypothesized that a comparison of the auditory and the visual tasks would only show differences in the sensory cortex, and that the uninstructed sorting task would show more activation related to executive functions than the instructed sorting task. Comparing average activation across all tasks with rest was hypothesized to show activity in dorsolateral PFC as well as parietal areas related to attention.

Modality Equivalence

The main effect of Modality did not show activations outside the sensory cortices, which can be interpreted as the AST being equivalent to the WCST when it comes to engaging the executive system.

Beauvais, Woods, Delaney, and Fein (2004) evaluated the validity of a tactile version of the WCST. They concluded that this version made for the visually impaired successfully differentiated between healthy and neurologically unhealthy persons. 80-89% of the neurologically and visually impaired were correctly classified by the tactile WCST. The present study only looked at healthy individuals, but at least for them, the Auditory WCST seems to be equivalent to the Visual WCST (see Figure 1).

Uninstructed Sorting Minus Instructed Sorting

The original idea behind using an instructed sorting task as a control condition for the sorting task was to cancel out activation related to maintaining information in working memory, while leaving in activation related to more purely executive functions, such as cognitive flexibility and inferential thinking. In the instructed task, the subjects were told along which dimension to compare the two stimuli. To solve this task, one needs to remember the instruction, apply attention towards the valid dimension, remember the value the first stimulus had along that dimension, then compare it to the value contained in the second stimulus. In the uninstructed sorting task, there was no instruction to remember, but in its stead there was a need to maintain a working hypothesis about what the valid rule was, and continually update this hypothesis as more feedback was acquired. Already at this point one could say that an assumption about the paradigm has been violated. The control condition was supposed to cancel out activation related to working memory maintenance when subtracted from the uninstructed condition. However, the uninstructed task lays a heavier memory load

on the subject, given that in addition to the sorting rule and the trial-by-trial stimuli, the subject has to remember which rules he or she has tested previously, and what feedback was acquired. A solution to this could be to add an extra item or several for the subject to remember in the instructed condition. The next issue to discuss are the executive functions hypothesised to be unique to the uninstructed task.

What is unique to the uninstructed task is the need to draw out the sorting rule by generating a hypothesis, testing it, and either changing it or confirming it. In addition to maintaining the necessary data, which was discussed in the previous paragraph, there is a need to simultaneously evaluate the possible inferences that can be drawn from the data and decide how to eliminate alternatives in the next trial. In order to do this, one needs to be able to sometimes keep a representation firm, and sometimes open it up and change it. To summarise, what is demanded to a greater degree in the uninstructed task includes close monitoring of contents in working memory and new, exogenous feedback, as well as flexibly producing and reiterating hypotheses regarding what the information means and what to do with it. Monitoring multiple items in working memory has been associated with the lateral PFC (Buschman et al., 2012; Petrides, 2000), while cognitive flexibility to a certain extent relies on the same underlying processes – having two thoughts at once is a prerequisite for changing one’s mind and for delicately responding differently to different contexts. But as have been seen from studies on bilinguals (Becker et al., 2016), on differences in response to sentence complexity (Prat & Just, 2010), and on monkeys learning new categories (Antzoulatos & Miller, 2011), cognitive flexibility, in terms of actually developing representations from the ground up, is predicated on an interplay between the PFC and the striatum.

The term ‘cognitive flexibility’ seems to sometimes refer to the ability to fluidly shift sets, and set-shifting tasks seem to be the type of task that engages the ACC in studies on

cognitive control (Botvinick et al., 2004). Whether this means that this definition of flexibility is equivalent to cognitive control, or that both flexibility and control are needed to solve set-shifting tasks is not entirely clear. At any rate, set-shifting tasks and cognitive control are associated with the ability to inhibit prepotent responses, as well as preparing an attentional set or a response set. Set shifting is required in both the instructed and the uninstructed task, since which stimuli to respond to changes within the same sorting rule (e.g. yellow triangles to yellow crosses, or two repetitions of “ba” to two repetitions of “pa”). It is probably still the case, however, that there are greater set-shifting demands in the uninstructed task, given that the subject’s inferences will change. In addition, the uninstructed task demands shifting between responding according to a hypothesised rule and developing said rule.

The pattern of activation seen when subtracting the instructed tasks from the uninstructed ones, resembles that of the DAN in Corbetta & Shulman (2002), especially so after applying the conjunction filter (see Figure 2 and Figure 4). This network was originally proposed to underlie the endogenous control of attention towards locations, features, or objects, as opposed to letting attention be exogenously captured by salient properties in the perceptual field. As mentioned above, shifting attentional set is a function expected to be engaged in both the uninstructed and the instructed tasks, but perhaps to a greater degree in the uninstructed ones. This task requires a recurring refocusing of attention between the different stimulus dimensions, the task feedback, and the hypothesising about which rule is currently in effect. The absence of any activation in dorsolateral PFC was a bit surprising, though, given this areas known contributions to monitoring of multiple items in working memory (Buschman et al., 2012; Petrides, 2000) and cognitive flexibility (Antzoulatos & Miller, 2011; Becker et al., 2016). Looking at the average activation across conditions compared to baseline, reveals the “missing” lateral PFC activation, covering both medial frontal gyrus and inferior frontal gyrus bilaterally (see Figure 5). This means that in the

contrast most relevant to the experimental design, activations in lateral PFC were subtracted out.

If the assumption should be held that the design and analysis of this experiment was flawless, then one would have to accede to the proposition that in these sorting tasks the lateral PFC is only involved in simple maintenance of items in working memory. This would, however, go against much literature stating that the storage of working memory representations is done elsewhere. It is also unlikely that even if the researchers did everything right that it is even possible to control for working memory without also subtracting out other functions, such as attention. Lebedev, Messinger, Kralik and Wise (2004) found that most neurons in PFC code for attended and not for remembered locations. Rushworth, Nixon, Eacott, and Passingham (1997) found that lesions to the ventral PFC in monkeys did not affect short term memory. D'Esposito and Postle (1999) reviewed eleven reports on memory span in patients with lesions to the dorsolateral PFC, and found that none of the 166 patients described showed significant deficits in this regard. So, if the presently reported subtracted out activation in PFC does not reflect short term memory maintenance, what does it reflect?

The prefrontal activation might just reflect the fact that the subjects were processing the trial information, while using the output of these computations to decide how to respond as well as whether or not to recruit the DAN to aid in the task. Even though the uninstructed task is clearly more difficult, the instructed task still demands some effort, as it is not an everyday thing to compare features in this way. Furthermore, one should assume that the subjects were trying their best to perform. If this is the case, then some of the functions uniquely engaged by the uninstructed task might have been camouflaged by this common activation, as they might not have demanded a sufficiently large haemodynamic response on top of the one already there from simply engaging with the tasks. There is no way at present

to determine whether the activation seen in the main contrast (uninstructed minus instructed) captures all the executive processes unique to the uninstructed task, but the possibility will still be entertained in the following sections.

Sustained attention has been difficult to separate from working memory in studies that have tried (Ikkai & Curtis, 2011; Jerde, Merriam, Riggall, Hedges, & Curtis, 2012; Ptak, Schnider, & Fellrath, 2017). The uninstructed task probably incurs a higher maintenance cost, despite efforts made to equalise. In addition, cognitive effort is associated with an increased need to inhibit irrelevant information (Haegens, Osipova, Oostenveld, & Jensen, 2009). The DAN partially performs its functions by inhibiting irrelevant information (Händel et al., 2011). Finally, flexibly switching between different stimulus-pair (or feature-pair) comparisons and reconfiguration of plan is likely to depend on a broad network of areas, which would increase the need for long-range synchrony and controlling which connections oscillate in phase with each other and which oscillate out of phase with each other. Given the DAN's already known involvement with modulating brainwaves across the brain in attention, motor intentions, and working memory, one can speculate that the activation seen in the present experiment reflects something like a conducting of cognition. Indeed, such phase-dependent oscillatory codes have been found in the communication between areas equal to or close to the FEF and IPS (Antzoulatos & Miller, 2016; Jacob, Hähnke, & Nieder, 2018; Salazar, Dotson, Bressler, & Gray, 2012). Whether the "higher level" operations needed to perform the WCST take place in a discrete area such as the dorsolateral PFC, or emerge through network interactions, is an open question. If the operations are coded in distinct phases of neural oscillations, then these might not necessitate a haemodynamic response where the operations are taking place (for example the PFC). However, in order for these oscillations to stay in rhythm while also flexibly fetching different items from working memory, the rhythms across the brain would have to be tightly controlled. A robust

haemodynamic response in the DAN would probably be seen both if the operations take place in the DAN itself and if the DAN is only supporting the PFC.

Compared with Lie, Specht, Marshall and Fink (2006), our results suggest activity more dorsally in the parietal lobe and more posteriorly, and slightly more laterally, in the frontal lobe. The tasks used in the present experiment differ from theirs in that it is actually a delayed matching task, while theirs more closely resembles the original WCST where the target stimulus and the reference stimuli are simultaneously present. The more ventral activation in parietal cortex around the temporoparietal junction in their study could reflect that visual attention was moving more between different stimuli. Lie et al. (2006) also reported activation in the ACC, which correlated with increasing task demands. In the present experiment, there was no activation in ACC in the Uninstructed minus Instructed contrast. It is possible that these differing results reflect that in their study, the subjects had to pick a response among four alternatives, while in the present experiment, only two alternatives were available. However, the fact that the ACC was equally involved in all conditions in the present experiment, while correlating with task demands in Lie et al. (2006) is puzzling. Comparing their image of the conjunction of each condition minus high-level baseline with the Positive effect of condition in the present experiment, yields very similar activations bilaterally in the dorsolateral PFC, IPS, SMA, and the ACC.

A frontoparietal pattern was also found by Specht, Lie, Shah, & Fink (2009), although their particular design revealed a laterality effect that the present study wasn't equipped to show.

Konishi et al. (1998) and Konishi et al. (1999) found activation bilaterally at posterior inferior frontal sulcus when subjects were shifting their cognitive sets. Although in our design we don't have the option of extracting the activation specific to set shifting, we also found activation at the intersection of precentral gyrus and inferior frontal sulcus.

Instructed Sorting Minus Uninstructed Sorting

As the pattern of activation left in the instructed sorting task after subtracting the activation of the uninstructed sorting tasks resembles the DMN (although less canonically than how the first contrast resembles the DAN), one might conjecture that the subjects had some mental resources left over even while giving responses to the instructed sorting tasks. These results should not be taken as evidence that working memory was not active, however, because such activity would have been cancelled out by the contrast used.

In the instructed sorting tasks, attention would only be needed to read the message stating which rule is currently in effect, and to compare the first with the second stimulus. Attention would be free to wander in between trials. In the uninstructed sorting tasks, however, attention would have to be given in between trials as well, because previous feedback would have to be maintained in order to interpret the next trial. Together with not having to switch between sets, this would relieve the need for a frontoparietal attention network to control attention and show up on the images. In the instructed sorting tasks, attention can flow naturally from rule notification to stimulus 1 to stimulus 2. In the uninstructed sorting tasks, however, attention has to be manually controlled to maintain previous feedback, then to the stimuli, and back again. Depending on how efficient a strategy the subject uses to solve the task, there could be several more switches. Switching is a complicated construct, though. On the face of it, one might think that it's simply about releasing a set or a representation, so that a new one can step in. But given what we know about the ACC and prepotent responses, it seems switching would also require a controlled inhibition of the pre-switch set. And of course, the post-switch set needs to be maintained as well.

Vatansever, Menon, and Stamatakis (2017) compared cerebral bloodflow between WCST and a control condition where the to-be-sorted cards were identical to one of the

reference cards. That study also showed recruitment of a frontoparietal network similar to the one reported here. However, Vatansever et al. (2017) hypothesised that these brain areas would be more active in the first five trials of every sorting rule, while the subjects were trying to figure out which rule was valid. They therefore proceeded to compare the BOLD contrast between trials 1-5 and trials 6-10, which confirmed the DAN's involvement in the early trials. The later trials, however, showed a larger effect in the DMN. Vatansever et al. (2017) attribute this to memory processes being more relevant to solving the later trials, and so they conclude that the DMN-activation reflects some kind of «autopilot» mode of responding when the sorting rule has been learned.

In a similar paradigm by Provost and Monchi (2015), it was also shown that the DMN becomes more active when performing the same task repeatedly over many trials. In that study, the subjects were always informed of which rule was currently valid, but in one condition the rule would change every trial, and in another it would stay the same for twelve trials in a row. Whether the DMN contributes to the execution of familiar tasks, or familiar tasks simply allow cognitive resources to be directed towards task-unrelated issues, was deemed an open question by Provost and Monchi (2015). The instructed sorting task in the present experiment is most similar to Provost and Monchi's (2015) repeated task condition, which is also reflected in the similar activations seen.

Regarding the Question of Whether the WCST is Suited to Detect Frontal Lesions

Both conditions show a clear frontal involvement compared to baseline, but the activation also covers a wide range of other areas. The present results therefore echo the sentiment that the WCST might very well be sensitive to frontal lesions, but in order to also be specific to frontal lesions, deficits associated with posterior areas would have to be

controlled for. However, the test could be used as an early marker for any deficits at all in executive function, since it requires the interplay of so many processes.

Strategy

Another factor contributing to performance on the WCST that has not been mentioned yet is the ability to perceive the logical contingencies required to interpret the feedback properly. When the previously correct sorting rule results in negative feedback, and you try a different rule which also results in negative feedback, you should try a third rule rather than revert to the original one. Failure to cycle through the rules in the most efficient order, can result in errors even after controlling for memory failure, distraction and inflexibility. There is also the possibility of getting hung up on the concrete levels of the dimensions, instead of the dimensions themselves. So that when receiving negative feedback for placing a yellow card in the yellow pile, the next trial you think you should try placing a green card in the green pile. Not interpreting the feedback correctly (thinking it was the particular colour that was pertinent, and not the higher level dimension) in this case leads to a misguided task set for the next trial, which can result in errors not explained by variation in memory, concentration or flexibility.

It is possible, however, that the process of testing out hypotheses about the sorting rule is simpler than what it seems like when trying to describe it. For example, testing out the hypothesis of colour being the rule only demands a button press and either mentally crossing out 'colour' if the feedback was negative, or settling into colour as an attentional set if the feedback was positive.

Thoughts on the Relation Between Executive Functions and the World We Inhabit

The executive functions are grouped by their common quality of sub-serving goal-directed behaviour through a concurrent consideration of personal goals and how these relate

to the many contexts a person inhabits. Sometimes the goals can be too sharply defined, as in the myopic schedules of people struggling with addictions. Other times the goals can be too vague, leading to nothing quite capturing your attention, as in ADHD. And yet other times, one can't separate the context from one's own goals, which might be part of the experience of schizophrenia. In Western societies today, each person is expected to set his or her own goals from a young age, and the expected arrival at these goals is often placed several years – sometimes decades – into the future. At the same time, one is expected to understand that everybody one meets has their own goals and reasons for acting the way they do, and that most everything one sees in a city was designed, produced, consumed, and, eventually, thrown away for any number of reasons. That living in an urban environment is a risk factor for developing schizophrenia is perhaps not so strange (McDonald & Murray, 2000). If the striatum codes for the behavioural relevance of things, and a dysregulated striatum produces psychosis, then what we refer to as 'reality' may very well be something fundamentally defined not objectively, but through intersubjective behavioural relevance. And if that is the case, then the social aspect of psychosis should not be underestimated.

Limitations

In order to uncover brain activity specifically related to executive functions beyond working memory storage functions, it's crucial to have a clear idea about which executive functions actually can be divorced from short term memory. After reviewing the literature, this has proved more difficult than expected. Although there are studies reporting such dissociations (Petrides, 2000), several theories about working memory emphasise how keeping information online is a result of there being a top-down signal "asking" for it (D'Esposito & Postle, 2015; Miller & Cohen, 2001). In addition, there is a strong possibility that so-called "higher" cognition always takes place within working memory, as the

manipulation of items in memory could be described as items in memory themselves. Finally, if working memory contents can be distinguished by their oscillatory signal, then maybe types of executive functions also are separated on this level - and not on a structural level. Future experiments on the research questions posed here would benefit from a thorough consideration of these possible confounds, and selecting hypotheses with clear implications with regards to theory.

One concrete recommendation for a future study would be to carefully count the number of items subjects would need to keep online, and adjust the control conditions accordingly. Another concrete recommendation addresses control processes. Since the control of responses may well be supported by the same processes that support the control of thoughts (Ptak et al., 2017), using a control condition where the subject does not submit overt responses could safeguard against this particular confound. The choosing of cards would then have to be done automatically by the computer, and in such a way as to provide the subject with just enough information to deduce the rule. Finally, the information value of fMRI-data can be enhanced by applying dynamic causal modelling, allowing for inferences to be made regarding the effective connectivity between clusters (Friston, 2011). At least one such study has been done showing different connectivity for working memory and cognitive control tasks, respectively (Harding, Yücel, Harrison, Pantelis, & Breakspear, 2015). If a theoretically grounded model for the effective connectivity seen in the present results can be produced, then applying dynamic causal modelling is recommended.

Conclusion

In this brief paper, fMRI-data have been analysed that were from an experiment investigating on the one hand, the neural equivalence of an auditory version of the WCST to the standard, visual WCST, and on the other hand, the neural substrates of performing the WCST when maintenance of information in short-term memory was controlled for. The

results support that this Auditory Sorting Test is indeed neurally equivalent to the WCST outside of modality-specific recruitment of sensory cortices. The neural substrate common to both AST and WCST covers the lateral prefrontal cortices, the anterior cingulate, the frontal eye fields, the supplementary motor area, anterior cingulate, as well as the intraparietal sulci. Exactly which roles the particular areas play in these tasks is left for future research to determine.

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