Time-based prospective memory in children and adolescents with 22q11.2 deletion syndrome

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Abstract

Objective: 22q11.2 deletion syndrome, also known as velo-cardio-facial syndrome (VCFS) is a genetic disorder caused by a microdeletion on chromosome 22q11.2 and characterized by marked impairment in visual attention and executive function. The present study examined if this cognitive deficit extends to prospective memory (the type of memory involved in remembering to perform actions in the future).

Method: 20 participants with 22q11.2DS aged between 6 and 14 were included in the study as well as 22 typically developing individuals (TDC) aged 6 to 12. To measure prospective memory, participants were asked to play a driving game (the *Dresden Cruiser,* Voigt et al., 2014). This time-based prospective memory task required children to remember to refuel their car when the fuel level was low by pressing a refuel button while driving.

Results and Discussion: Participants with 22q11.2DS remembered less often to refuel the car. Furthermore, participants with 22q11.2DS checked the fuel gauge significantly less often than the controls.

Conclusions: Participants with 22q11.2DS therefore demonstrate difficulties completing a time-based prospective memory task. This can be explained by a generally less frequent time checking behaviour in comparison to TDC.

Keywords: Prospective memory, 22q11.2 deletion syndrome, Time checking.

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Introduction

22q11.2 deletion syndrome (22q11.2DS), also known as velo-cardio-facial syndrome (VCFS), is a genetic disorder caused by a microdeletion on chromosome 22q11.2, estimated to occur in one of every 6000 live births (e.g., Botto et al., 2003). Most school-aged children with 22q11.2DS have lower than typical full scale IQ with borderline intellectual function (FSIQ 70-75) (Karayiorgou, Simon, & Gogos, 2010). In late adolescence and early adulthood, up to one-third of people with 22q11.2DS develop schizophrenia or schizoaffective disorder (see Schneider et al., 2014, for a review including over 1400 patients).

A number of studies have explored structural brain differences in 22q11.2 DS, typically reporting reduced brain volume (between 8% and 11% smaller than typically developing controls). Most neuroimaging studies report a reduction in total hippocampal volume (Debbané, Glaser, David, Feinstein, & Eliez, 2006; Deboer, Wu, Lee, & Simon, 2007; Flahault, Schaer, Ottet, Debbané, & Eliez, 2012; Kates et al., 2006). According to Flahault et al. (2012) this reduction in volume could be due to a reduction in the amount of input received from connected cortical regions such as the parieto-lateral cortex, the posterior cingulate and the temporal cortical structures, known also to be reduced in 22q11.2DS. Brain function in 22q11.2DS is affected by reduced gene-dosage of more than one gene. For example, DGCR8 (DiGeorge syndrome critical region 8), PRODH (proline dehydrogenase) or COMT (catechol-O-methyltransferase) have been linked to neural changes and cognitive deficits (see Karayiorgou et al., 2010, for a review).

Besides these structural brain abnormalities, many studies have also attempted to better define cognitive functioning in 22q11.2DS (for a review, see Biswas & Furniss, 2016). The

main findings so far suggest a specific cognitive phenotype and not merely a lower IQ more generally. For example, performance in reading is better than in mathematics, with specific difficulties in resolution of problems including spatial, temporal or numerical information (Sobin et al., 2004). Studies have also assessed executive functioning and report that people with the 22q11.2 deletion syndrome have marked impairment in visual attention and executive function (Maeder et al., 2016; Sobin et al., 2004; Sobin, Kiley-Brabeck, & Karayiorgou, 2005). Shapiro, Tassone, Choudhary, and Simon (2014) point to deficits in response inhibition, cognitive flexibility, and working memory. Several studies report working memory impairments in children and adolescents with 22q11.2 DS (Bearden et al., 2001; Kates et al., 2007; Lajiness-O'Neill et al., 2005; Montojo et al., 2014; Sanders, Hobbs, Stephenson, Laird, & Beaton, 2017; Simon, Bearden, Mc-Ginn, & Zackai, 2005). Maeder et al. (2016) showed atypical developmental trajectories for working memory and verbal fluency, suggesting different developmental patterns of these executive functions in 22q11.2 DS. Azuma et al. (2009) also showed that differences in brain activation (parietal and occipital regions) explained deficits on a visuospatial working memory task, thus suggesting that differences in the development of specific brain structures might underpin the cognitive deficits in this population.

This study focuses on memory. To the best of our knowledge, studies so far have only explored retrospective memory in 22q11.2DS, which is the ability to remember something from the past (words, people, events, etc.). First of all, the existing literature suggests better performance on verbal than on visuospatial memory tasks (Wong, Riggins, Harvey, Cabaral, & Simon, 2014; Woodin et al., 2001). People with 22q11.2DS have difficulties in memorizing faces, shapes, line orientation or spatial localizations (Gur et al., 2014; Woodin et al., 2001),

with greater difficulties in remembering faces or objects than localizations (Bostelmann et al., 2016; Campbell et al., 2010; Vicari et al., 2012). Studies exploring episodic memory (i.e. the ability to retrieve recently learned episodes such as a list of words) report relatively spared performance in 22q11.2DS. For example, some studies suggest that people with 22q11.2 DS (adolescents and adults) demonstrate similar levels of recognition performance to healthy controls for materials such as words, pictures or even action statements (Debbané, Glaser, & Eliez, 2008; Debbané, Van der Linden, Glaser, & Eliez, 2008). Two studies also reported intact rote verbal recall (Woodin et al., 2001), and story and word recall (Lajiness-O'Neill et al., 2005). However, other studies showed deficits in contextual information leading to source confusion errors suggesting that memory deficits in this population are possibly due to difficulties in binding contextual information to gist information. In other words, episodic memory in 22q11.2 DS could be characterized by a deficit in retrieval of contextual information associated with memory content.

The novelty of this study is to explore prospective memory in 22q11.2DS. Prospective memory (PM) refers to the type of memory involved in remembering to perform actions in the future (Einstein & McDaniel, 1990). It combines executive processes (executing the action at the appropriate time) with memory processes (remembering the content of an intention) (Mahy, Moses, & Kliegel, 2014). Typical examples (in children) are remembering to return homework or remembering to reply to a birthday invitation and (in adults) to take the right medication at the right time. PM therefore plays a key role in everyday life and has been shown to be related to activities of daily living in adults (Woods, Weinborn, Velnoweth, Rooney, & Bucks, 2012). Typically, PM is investigated by giving participants PM instructions to complete while working on an ongoing task (Einstein & McDaniel, 1990). It comprises two

components; a retrospective component (ability to recall the PM instructions) and a prospective component (performing an action in response to a cue) (Einstein & McDaniel, 1990). Einstein and McDaniel (1990) also distinguish between event-based and time-based PM. Time-based PM involves initiation of an activity at a given time or after a certain time has elapsed, whereas event-based PM involves initiating an action in response to an external target cue. In contrast to event-based PM where an external target event prompts the intention, time-based PM relies on self-initiation of the intended action (Mäntylä, Carelli, & Forman, 2007). Hence, it is crucial that the passage of time is strategically monitored (e.g., Mackinlay, Kliegel, & Mäntylä, 2009), which implies executively demanding processes.

PM is an ability that is detectable as early as 3 years of age (Kliegel & Jäger, 2007). Both event-and time-based PM performance improve across childhood, and even into adolescence (Kliegel & Jäger, 2007; Kvavilashvili, Messer, & Ebdon, 2001). This developmental trend is interesting given that PM plays a key role in independent living (Kliegel & Martin, 2003). The most noticeable memory errors in our everyday lives, or at least the ones with the most direct impact in everyday life would probably be PM errors and not retrospective memory errors. As a result, because PM failure could be a threat to an individual's independence, safety or even health, several studies have begun to look at PM performance in clinical populations. Of particular interest to the present study, PM has been found to be impaired in autism (Henry et al., 2014), ADHD (Altgassen, Kretschmer, & Kliegel, 2014), and schizophrenia (Ordemann, Opper, & Davalos, 2014), which are all commonly found in 22q11.2DS (Biswas & Furniss, 2016). However, to the best of our knowledge, PM has not been explored in 22q11.2DS.

The present study had the main goal of determining whether or not PM impairments are part of the cognitive phenotype that can be found in 22q11.2DS. On a clinical level, such an investigation might help carers and patients to have more realistic expectations in terms of how well these patients can remember future events, such as taking their medication. The cognitive phenotype observed in 22q11.2DS would lead us to predict PM failures. Successful PM combines retrospective memory processes and a prospective component related to executive function and working memory (executing the action at the appropriate time). Whilst previous findings in schizophrenia (Ordemann et al., 2014), autism (Henry et al., 2014), or ADHD (Altgassen et al., 2014) lead us to predict that PM will be impaired in people with 22q11.2.DS, the memory phenotype found in 22q11.2DS suggests that this PM impairment will not be due to retrospective memory difficulties. Several studies have shown that verbal memory, recall or recognition of words or stories, is mostly preserved in 22q11.2DS (Debbané, Glaser, et al., 2008; Debbané, Van der Linden, et al., 2008; Lajiness-O'Neill et al., 2005; Woodin et al., 2001). In other words, any PM deficit in 22q11.2DS is unlikely to be due to participants forgetting the instructions. Rather we suggest that people with 22q11.2DS might show PM deficits due to difficulties managing the prospective component of the task, which requires time managing or time monitoring. In a paper on multitasking, Schneider et al. (2016) found that people with 22q11.2DS checked the time less frequently than controls during the tasks. For this reason, time-based PM might be more sensitive than event-based PM to detect PM impairments in 22q11.2DS as it requires controlled checking behaviours. Time-based PM was therefore the central measure used in the current study.

Method

Participants. 20 participants with 22q11.2DS aged between 6 and 14 were included in the current study (mean age = 10.70 +/- 2.31). Individuals with 22q11.2DS were recruited through the Dijon Hospital genetic centre and French-speaking parent associations in Geneva. The presence of a 22q11.2 was confirmed using Fluorescent in Situ Hybridization (FISH) or Quantitative Fluorescence Polymerase Chain reaction (QF-PCR). Some patients met diagnostic criteria for psychiatric conditions (1 major depression, 5 simple phobia, 7 generalized anxiety disorder, 6 ADHD) and 6 participants were under medication at the time of testing (2 taking antipsychotics, 4 taking Methylphenidate).

Twenty-two typically developing individuals (TDC) aged 6 to 12 (mean age= 10.63 +/- 2.01) also participated in the study. The exclusion criterion for TD participants was the presence of any learning or behavioral/psychiatric disorder. Typically developing individuals were recruited via local kindergartens, primary and secondary schools.

Both groups were matched for age ($F(1, 40) = 0.009$, $p = .925$) and gender distribution ($F(1,40) = .644$, $p = .427$) – one way ANOVAS on these measures did not reveal any group differences. Mean full-scale IQ was 71.6 (*SD* = 10.8) in patients with 22q11.2DS, but was not measured in control participants.

All participants were tested in a quiet room at the hospital and all mandatory laboratory health and safety procedures were adhered to within the course of conducting the experimental work reported here. Written informed consent was obtained from participants and their parents according to protocols approved by the Central Research Ethics Committee of Geneva (IRB number: PB-2016-01470) and by the local ethics committee for Dijon University.

Prospective Memory task.

Ongoing Task component. The *PM task* was the *Dresden Cruiser* (Voigt et al., 2014), a driving simulation game originally developed by Kerns (2000) that requires children to drive a target vehicle on a road without crashing into other cars. The car drove on a two-dimensional road displayed vertically on a computer monitor, consisting of three parallel lanes, with other vehicles driving in the same direction on the road. The ongoing task required participants to pass the other cars without hitting them in order to earn points. A score was permanently displayed in the lower right corner of the screen during the game to increase children's motivation. To account for differences in ongoing task performance, the difficulty of the driving game was adapted to each participant's individual performance level (number of car crashes) on a baseline block (Kvavilashvili, Kyle, & Messer, 2008). There were five difficulty levels of the *Dresden Cruiser* that varied the number of other cars presented on the road per minute (ranging from 25 to 65 cars per minute). Before starting the baseline task, participants underwent a practice trial to ensure understanding of the task. The instructions were simple to understand: children were asked to play a car game and pass other cars to earn points. They were also informed that they would lose 100 points if they crashed into another car. Children were therefore told to avoid crashes to earn as many points as possible. Points already achieved appeared in the right corner of the screen. Children were given a practice trial and shown that the car was maneuvered with two arrows, the arrow on the left to go left and the arrow on the right to go right.

Prospective Memory Task component. The time-based PM task required children to remember to refuel their car when the fuel level was low by pressing a refuel button while

driving. The fuel level was displayed on a fuel gauge that children could check by pressing a button (which would reveal the fuel gauge for three seconds in the left corner of the screen). By pressing a second button on the gamepad, participants could refuel the car whenever the fuel gauge dropped into the red area (indicating that the tank was less than 1/6 full). To increase task motivation, children received 100 additional points each time they refuelled the car within the appropriate timeframe (in comparison, participants only received 33 points for passing a car). If the car ran out of fuel, the tank was refilled automatically without any signal to indicate that there was a failure to refuel. A test block consisted of four one-minute trials and thus four opportunities to complete the PM task. There were two test blocks. In each trial, the car had to be refilled after 50 seconds of driving (when the fuel gauge indicated the tank was only 1/6th full) and within 10 seconds (before the tank was refilled automatically). Participants were not given any information about the temporal characteristics of the task. Participants were given a practice trial before the actual task and were told that they would play the car game several times. In this, they were reminded of the fact that they were not supposed to crash into other cars, and to check the amount of points in the right corner of the screen. After the practice trial, they were also told that from now on they would have to not hit other cars *and* make sure that their car always had enough fuel. To check how much fuel they had left, children had to press a yellow key on the keyboard. If the needle was in the red area of the fuel gauge, it meant that the car needed more fuel. Children were told that they would earn 100 points for refueling the car at the right time. Children were also explained that if they forgot to refuel and the tank was completely empty, it will be refueled automatically, but they will not gain any additional points.

Procedure. Children were tested individually in a single 15- to 30-minute testing session. Figure 1 shows a diagram of the order in which tasks were carried out. First, children were given the instructions explaining the task and then practiced the ongoing task (1 minute) to familiarize themselves with the driving component of the game. Then, children were asked to 'play again' for 4 minutes (baseline block). On the basis of the children's baseline performance, a difficulty level for the ongoing task was chosen for the two following PM tasks. The cruiser had five difficulty levels ranging from 1 (95 cars) to 5 (271 cars). On the basis of their baseline performance, the average level chosen for the children with 22q11.2 DS was 2.4 (150 cars) ranging from 2 to 3 whilst the average level for the controls was 4.5 (250 cars) ranging from 3 to 5. The children were then given the PM instructions and were also asked to recall the instructions to ensure accurate understanding.

As suggested by Ellis and Kvavilashvili (2000), a delay between task instructions and subsequent execution of the PM task was implemented. Children were asked to complete dot-to-dot puzzles (connecting dots to make a shape appear) for 5 minutes. Then children were asked to complete the first PM test block without any reminding of the need to refuel. Afterwards, children were reminded of the instructions for the PM task and asked to play dot-to-dot again for 5 minutes before performing the second PM block. After children had completed the *Dresden Cruiser*, they were asked to recall the instructions and only children who could recall the PM task instructions were included in the data analysis. In this study, all tested children were able to recall the PM instructions and were all therefore included.

(Insert Figure 1 here)

Results

Ongoing task performance in the PM task was measured by the number of crashes (Hit count). A one-way ANOVA revealed no group difference on this measure ($F(1,40) = 0.003$, $p = .954$, $\eta^2 = .000$) therefore showing that ongoing task difficulty was comparable for both groups ($M = 39.58$, $SD = 14.02$ for 22q11.2, $M = 39.84$, $SD = 14.20$ for TDC).

PM performance was analysed using the number of correct on-time refuels across the two blocks (maximum score of 8). A one-way ANOVA showed a significant group effect, with control participants ($M = 3.13$, $SD = 1.03$) remembering to refuel the car more often than the participants with 22q11.2DS ($M = 2.01$, $SD = 1.35$), $F(1,40) = 9.145$, $p = .004$, $\eta^2 = .186$. To determine whether PM deficits could be considered as a specific cognitive trait beyond the global effect of intellectual disability, correlations between PM performance and IQ were carried out in the group of participants with 22q11.2DS. The correlation between IQ and the PM measure (number of correct on-time refuels) was found to be non-significant in the group of participants with 22q11.2DS ($r = .092$, $p = .736$).

Time monitoring. Furthermore, to gain insight into the processes underlying the observed PM deficit, time monitoring was analysed in two different ways. First, as in previous studies (Mäntylä et al., 2007) analyses focused on the total number of fuel gauge checks across the two blocks. The one-way ANOVA here revealed a significant group effect ($F(1,40) = 10.77$, $p = .002$, $\eta^2 = .212$), showing that participants with 22q11.2DS checked the fuel gauge significantly less often than the controls, with an average of 11.9 checks for the controls compared to 7.9 for the participants with 22q11.2DS.

Second, following the standard procedure in analysing time monitoring patterns (e.g., Kerns, 2000; Kliegel et al., 2005), the number of gauge checks across the length of one trial was analysed by dividing it into four intervals (see Figure 2). Following Mahy et al. (2015), the average number of gauge checks within the first three intervals was compared with the average number of gauge checks in the fourth interval directly preceding the PM target time. Strategic monitoring would be reflected by a higher number of gauge checks in the fourth interval compared to earlier gauge checks. A 2 (Time interval: first three vs. fourth interval) x 2 (Group) ANOVA first confirmed a significant group effect ($F(1,40) = 8,18$, $p = .007$, $\eta^2 = .170$) showing that overall participants with 22q11.2DS monitored the time less often than typically developing children. On average, in the first interval, control participants checked the gauge 1.9 times against 1.17 for the 22q11.2.DS participants. In the second interval, controls checked the gauge on average 2.5 times against 1.3 for the 22q11.2DS participants. In the third interval, the control participants checked the gauge on average 4.04 times and the 22q11.2DS 1.4 times. For the fourth interval, control participants checked the gauge 4.3 times and the 22Q11.2DS 3.22 times. Furthermore, on average, control participants checked the time every 21.8 seconds (SD=12, 61) against 29.87 seconds for the 22q11.2 DS group (DS=19,95). The two-way ANOVA also revealed a significant effect of time interval ($F(1,40) = 34.14$, $p < .001$, $\eta^2 = .460$), with more checks in the final interval compared to the first three intervals in both groups. No significant interaction between Group and Time interval was found.

(Insert Figure 2 here)

Prospective memory and time monitoring. To further explore the relation between monitoring and PM performance, correlations were carried out between the PM measure (number of correct on-time refuels) and the total number of fuel gauge checks. The results showed that for both groups, monitoring the gauge was clearly linked to PM performance (r = .568, p = .006 for controls; r = .643, p = .002 for participants with 22q11.2DS). This is in line with other studies on time-based PM in children (e.g., Mackinlay et al., 2009).

Discussion

The current study revealed time-based PM deficits in 22q11.2DS. First, results showed that participants with 22q11.2DS remembered less often to refuel the car, therefore failing to execute the PM action. It is important to note here that all participants were able to recall the instructions, insuring that the PM failure could not be due to forgetting what the action to perform was, and therefore we can rule out that this was due to a retrospective memory failure. That is, all participants including participants with 22q11.2DS correctly recalled the instructions. Furthermore, the PM failure found in this study cannot be explained by differences in difficulty levels of the ongoing task, as the PM task level was chosen on the participants' baseline performance on the ongoing task and the results showed no group differences on the ongoing task.

Second, participants with 22q11.2DS were found to check the fuel gauge significantly less often than the controls. This deficient checking behaviour is in agreement with what Schneider et al. (2016) observed in a study on multitasking in which adolescents with 22q11.2DS were found to check the time less often (note, however, that PM needs to be

differentiated from multitasking, see McDaniel & Einstein, 2007, for more details). Furthermore, the results showed that PM performance was clearly correlated with the number of fuel gauge checks, suggesting that low PM performance is directly linked to a failure to check the gauge. This deficient checking behaviour could somehow be due to group differences in motivation. Control participants, in comparison to children with 22q11.2DS, might be more sensitive to, and therefore more motivated by, a reward system based on points. That is, failure to check the gauge in children with 22q11.2DS might reflect more a lack of initiation due to motivational problems than a real difficulty in PM. This is in accordance with the literature showing negative symptoms including a lack of motivation in people with 22q11.2DS (Schneider et al., 2012; Schneider et al., 2014). According to this reasoning, one possible limitation of the current study is that the failure to refuel did not result in any penalty in this task. The car continues to run without fuel and the tank is refuelled automatically (this was done in order to not provide an additional reminder of the PM task). Therefore, children with 22q11.2DS might have focused on the ongoing task to try and reduce the number of car crashes which, as opposed to forgetting to refuel, could have resulted in major loss of points. This means a priority is to test for potential group differences in motivation. Future studies should also explore the link with general intelligence, by for example comparing groups with different IQ levels, although it should be pointed out that in the current study no correlations were found between IQ and PM performance in the group of 22q11.2DS participants. Furthermore, the marked increase in monitoring (number of gauge checks) in the final interval, for both groups, suggests that all participants, including participants with 22q11.2DS, were able to anticipate the target time correctly and use a strategic monitoring behaviour in response. According to Mahy et al. (2015), this increase in monitoring reflects a proactive time monitoring strategy. Therefore,

this study suggests that people with 22q11.2DS are able to monitor the passage of time to some extent and to proactively regulate their monitoring behaviour, as found in studies on TDC (Kerns, 2000; Voigt et al., 2014). This is interesting considering that Debbané, Glaser, Gex-Fabry, and Eliez (2005), with a larger sample and therefore more statistical power, showed that time perception was impaired in 22q11.2DS. However, it could be argued here that the more naturalistic PM task used in this experiment facilitated time perception.

To conclude, this study shows that children and adolescents with 22q11.2DS have difficulties completing a time-based PM task. This can be explained by the patient group less frequently checking time in comparison to controls. However, it is important to note that children and adolescents with 22q11.2DS both demonstrated an increase in gauge checks closer to the target time reflecting, some preservation of strategic time monitoring. Thus, PM deficits were not caused by proactive control impairments.

According to Mahy et al. (2014), PM performance is modulated by different factors such as the nature of the intention, the length and nature of the delay before the PM task, the nature of the ongoing task, and the nature of the prospective cues. These factors would impact on PM performance via their effect on executive function. In line with this theoretical framework, the observed PM deficits might be explained by group differences in working memory performance. For example, one could suggest that children and adolescents with 22q11.2DS remember the task and check the gauge but then the intention to press the right key to refuel would slip out of their working memory. To explore this question, in a further study, working memory load could be manipulated (see Voigt et al., 2014). They could also struggle to inhibit the ongoing task response or fail to shift between two tasks, (see

Schnitzsphan et al., 2013 for an example of a relation between these two facets of executive function and PM in aging). From our point of view, future studies should consider all three executive function facets, as well as potential motivation differences. Finally, having found evidence of impaired PM, and PM being highly important in everyday life, future studies should explore the potential relationship between PM deficits, behavioural problems in 22q11.2DS and psychiatric diagnosis.

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