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Developmental trajectories and brain correlates of Directed Forgetting in 22q11.2 deletion syndrome

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Abstract 22q11.2 deletion syndrome (22q11DS), also known as velo-cardio-facial syndrome (VCFS) is the most common copy number variant (CNV) in humans caused by a microdeletion on chromosome 22q11.2. The phenotype encompasses heart anomalies, cleft palate and cognitive difficulties. Alongside brain differences in VCFS, such as reduced hippocampal volume, different cognitive developmental trajectories can be observed. The aim of this study was to explore the developmental trajectories of cognitive inhibition in memory using longitudinal data acquired in a large cohort of individuals with 22q11DS and the brain correlates to those developmental changes. 51 participants with 22q11DS (mean age: 13.75 ± 4.26 , mean IQ score: 70.50 ± 10.75) and 43 typically developing individuals matched for age ($M = 13.50 \pm 4.91$) and gender were recruited. To explore inhibition in memory, the Directed Forgetting paradigm was used. 30 words were presented, half were 'To be remembered items'(TBR) and the other half 'To be forgotten items' (TBF). To measure source memory, participants were asked during the recognition stage to say if the word was a TBR or a TBF item. Participants were tested during two consecutive visits, with a mean interval of 3 years. T1-weighted images were acquired using a 1.5T Philips or a 3T Siemens scanner at both visits. Both groups recognized more TBR than TBF items (Directed forgetting effect), however, participants with 22q11DS recognized fewer TBR items and did not show an increased recognition of TBR items with age. Furthermore, in participants with VCFS increased source memory errors with age was associated with a decline in hippocampal volume.

Key words: 22q11.2 deletion syndrome, longitudinal study, Directed Forgetting, Memory, Hippocampus

1. Introduction

22q11.2 deletion syndrome (22q11DS), also known as velo-cardio-facial syndrome (VCFS), is a genetic disorder caused by a microdeletion on chromosome 22q11.2, with a prevalence of 1:20,000 to 1:40,000 (Oskarsdottir, Vujic, and Fasth, 2004, Shprintzen, 2005; Grati, Molina Gomes, Ferreira, Dupont, Alesi et al., 2015; McDonald-McGinn, Sullivan, Marino, Philip, Swillen, Vortsaam et al., 2015). The phenotype often encompasses heart anomalies, cleft palate and cognitive difficulties. Most school-aged children with 22q11DS have lower than typical full scale IQ with borderline intellectual function (FSIQ 70-75) (Karayiorgou, Simon, & Gogos, 2010). However, most studies suggest a specific cognitive phenotype (for a review, see Biswas & Furniss, 2016, Moberg, Richman, Roalf, Morse, Graefe et al., 2018) with, for example, specific difficulties in problem resolution including spatial, temporal or numerical information (Sobin, Kiley-Brabeck, Daniels, Blundell, Anyane-Yeboah et al., 2004), attentional and executive deficits (Maeder, Schneider, Bostelman, Debbané, Glaser et al., 2016; Sobin et al., 2004; Sobin, Kiley-Brabeck, & Karayiorgou, 2005). Individuals with 22q11DS also typically display a combination of spared and impaired memory performance, with better performance on verbal than visuospatial memory tasks (Wong, Riggins, Harvey, Cabaral, & Simon, 2014; Woodin, Wang, Aleman, McDonald-McGinn, Zackai & Moss., 2001). The novelty of this study is to focus on forgetting with the aim to explore the developmental trajectories of intentional forgetting using longitudinal data acquired in a large cohort of individuals with 22q11DS.

Forgetting is a memory process that usually seems rather passive. However, intentional forgetting is in everyday life sometimes necessary when information does not need to be encoded, such as when needing to update information stored in memory to respond to a change in goals, like 'forgetting' the previous platform number of your train when it has been announced that there is a new one. Experimentally, such intentional forgetting can be investigated using the directed-forgetting paradigm (for reviews see

Johnson, 1994 and Macleod, 1998). In the directed forgetting paradigm, participants are presented with a list of items that they are instructed to either remember for a later memory test (these items are labelled To Be Remembered (TBR) items) or to forget (these items are labelled To Be Forgotten (TBF) items). The cue to forget or to remember can be applied either on an item-by-item basis and therefore to each item individually (item-method directed forgetting) or to an entire list (list-method directed forgetting) (Bjork, 1972). The Directed forgetting effect (DF) is that TBR items (or words in the list) are better remembered than TBF items. Item-method directed forgetting is supposed to reflect inhibition processes happening at encoding (Zacks & Hasher, 1994), whilst the list-method offers a retrieval-inhibition account (Bjork, 1989) of the DF effect. Item-method DF is also proposed to reflect selective encoding processes favouring TBR items (Bjork, 1972; Basden & Basden, 1996). In other words, when presented with TBR items, participants will instigate a deeper encoding of the items. The DF paradigm offers an excellent opportunity to explore selective forgetting and inhibitory processes in episodic memory and has therefore been widely used in developmental studies or in clinical groups. Individuals with 22q11DS were found to show a preserved DF effect using an item-method paradigm, suggesting that participants with 22q11DS are therefore able to inhibit the TBF items at encoding allowing for the release of processing resources then applied to more elaborate encoding of TBR items (Debbané, Glaser and Eliez, 2008).

Following this first indication that intentional forgetting would be preserved in participants with 22q11DS, the question was raised of the developmental aspect of intentional forgetting in this clinical population. Indeed, a number of studies using the DF paradigm confirmed the existence of a developmental trend during mid-to late childhood, showing that the ability to intentionally inhibit the maintenance and recall of irrelevant information improves with age, using both item-method and list-method (Bray, Turner & Hersh 1985; Harnishfeger & Pope, 1996; Todor, 2012). Our question is therefore to determine whether or not such a

developmental pattern would be observed in children with 22q11DS. Indeed, despite the fact that developmental trajectories of cognitive functions in 22q11DS have rarely been explored, several studies for example show that the discrepancy observed between verbal and perceptual abilities, favouring the verbal domain, changes with age and the VIQ > PIQ cognitive profile in children seems to change with age such that such a discrepancy is less common in adolescence (e.g. Campbell and Swillen, 2005). Furthermore, a decline in IQ scores has been found in several studies, suggesting a cognitive decline with age in 22q11DS (Gothelf, Eliez, Thompson, Hinard, Penniman, Feinstein et al., 2005; Green, Gothelf, Glaser, Debbane, Frisch, Kotler et al., 2009, Vorstman, Breetvelt, Duijff, Eliez, Schneider, Jalbrzikowski et al., 2015). A longitudinal study by Maeder et al. (2016) showed atypical developmental trajectories in the 22q11DS group for working memory and verbal fluency (see Bostelmann, Schneider, Padula, Maeder, Schaer, Scariati et al., 2016 for similar findings on verbal fluency). However, no such results were found for cognitive or motor inhibition, as measured by the Conner's Continuous Performance Test (CPT, Conners & Staff, 2000) and the Stroop test (Stroop, 1935) respectively.

The novelty of the current study is to assess the question of an atypical developmental trajectory of intentional forgetting in 22q11DS using the Directed Forgetting paradigm. Furthermore, to address whether differences in developmental trajectories in intentional forgetting might occur due to differences in remembering the to-be-remembered (TBR) and to-be-forgotten (TBF) cues given at encoding, the novelty of this study was also to ask participants whether the items had been presented as TBR items or TBF items. In other words, this procedure allowed to measure whether source memory was impaired in 22q11DS using the Directed Forgetting paradigm. Despite this procedure being novel, it is noticeable that many researchers have already combined judgments of source with memory judgments (Conway and Dewhurst, 1995; Hicks et al., 2002; Meiser and Broöder, 2002; Meiser and

Sattler, 2007; Perfect et al., 1996) showing for example that Remember responses are associated with source recall, (Humphreys et al., 2003 ; Meiser and Broder, 2002; Perfect et al., 1996 ; Souchay et al., 2013). The reason to follow a similar procedure in the current study was that previous studies had already pointed towards a possible source memory deficit in this clinical population. For example, Debbané et al. (2008), explored source memory using an action monitoring paradigm (Laroi, Collignon & Van der Linden, 2005), in which participants were asked to imagine an action performed by themselves or an experimenter. Results show that adolescents with 22q11DS show a similar level of hits in the recognition task but committed more source confusion errors and therefore struggled to remember who actually performed the action. These findings suggest that episodic memory in 22q11DS could be characterized by a deficit in retrieval of contextual information associated with memory content.

The second aim of this study was to determine the neural correlates of intentional forgetting in individuals with 22q11DS in a developmental perspective. Indeed, patients with 22q11DS show a wide range of neurological impairments including in frontal brain regions (for a review see for instance Scariati, Schaer, Karahanoglu, Schneider, Richardi, Debbané et al., 2016), that may underlie alterations in inhibitory processes. Reduced brain volume and cortical thickness (CT) has been reported in patients with 22q11DS in cross-sectional studies reporting widespread increased CT in this clinical population (Sun, Ching, Lin, Forsyth, et al., 2018). However, in regards to the important structural changes during normative brain development, longitudinal studies of CT seem more appropriate. Longitudinal studies of brain volume or CT are still very few and provided some unclear findings (Schaer et al, 2009; Radoeva, Bansal, Antshel, Fremont, Peterson et al, 2017; Kates, Antshel, Faraone, Fremont et al, 2011). However, of particular interest to this study, altered developmental trajectories of the frontal cortex have been reported by two longitudinal investigations (Schaer, Debbané,

Bach Cuadra, Ottet, Glaser, Thiran et al., 2009; Radoeva, Bansal, Antshel, Fremont, Peterson & Kates, 2016). These studies show that while children affected by the 22q11 deletion have a thicker cortex as compared to controls, they undergo a faster cortical thinning during adolescence, which leads to an excessive reduction of thickness by adulthood. Similarly, a reduction in total hippocampal volume (Debbané, Glaser, David, Feinstein, & Eliez, 2006; Deboer, Wu, Lee, & Simon, 2007; Flahault, Schaer, Ottet, Debbané, & Eliez, 2012; Kates, Miller, Abdulsabur, Antshel, Conchelos, Fremont & Roizen, 2006; Mancini, Sandini, Paluda, Züller, Schneider, Schaer & Eliez, 2020), might lead to inhibitory failure or cue association in the DF paradigm in patients with 22q11DS. Of particular interest to this study, activity in the hippocampus was found for intentional forgetting of TBF items (Nowicka, Marchewka, Jednorog, Tacikowski & Brechmann, 2011; Wylie, Foxe & Taylor, 2008). Furthermore, right prefrontal brain activity has also been implicated in inhibitory control processes (Anderson, Ochsner, Kuhl, Cooper, Robertson, Gabrieli et al., 2004; Rizio & Denis, 2013) and the right superior/middle frontal gyrus seems differentially activated when information is cued to be forgotten compared to when it is cued to be remembered (Nowicka et al., 2011; Wylie et al., 2008; Yang, Liu, Xiao, Li, Zeng, Qiu & Zhang, 2011). To summarize, the present study describes the first attempt to explore developmental trajectories of intentional forgetting in 22q11.2 deletion syndrome and the brain correlates to those developmental changes. The neuroimaging findings in volume and CT in patients with 22q11.2 deletion syndrome and the similarities with between the regions altered and the regions involved in directed forgetting lead us to analyze the relationship between volume, CT and DF effect in this clinical population. This approach will also provide further knowledge of brain development using a longitudinal approach.

2.Results

2.1 Statistical analyses on behavioural measures. Statistical analyses were performed on hit rate $((\text{hits}+0.5)/(\text{hits} + \text{misses} + 1)) \times 100$, false alarm rate $((\text{false alarms} + 0.5)/(\text{false alarms} + \text{correct rejection} + 1)) \times 100$, TBR cues (proportion of source attribution errors for TBR items) and TBF cues proportion of source attribution errors for TBF items. DF effects were estimated by repeated-measures analyses of variance (ANOVA), with TBR correct recognition scores (TBR items correctly recognized on a possibility of 15 items) and TBF correct recognition scores (TBF items correctly recognized on a possibility of 15 items) as dependent variables, with group as a between subject variable, and time of testing as a within group variable.

Although repeated-measures ANOVAs are adequate for the analysis of longitudinal data, they are limited to fully explore the developmental trajectory of a cognitive process that is known to evolve between childhood and adulthood. For this reason, we also performed more complex analyses using mixed model regression analyses (Mutlu et al., 2013). These models are particularly appropriate when participants are assessed at different ages and with a variable time interval between the assessments. Using an algorithm developed by our group and described in details in Mutlu et al. (2013), random-intercept models were fitted to the data using Matlab R2017a. Within-subject variables (i.e. performance on the Directed Forgetting paradigm) were modelled as random effects, and population variables (i.e. diagnosis, age, and their interaction) were modelled as fixed effects. The simplest model (e.g. a constant model) was always fitted first using the `nlmefit` function and was compared against a more complex model (e.g. a linear model). If the more complex model was a significantly better fit to the data according to the Bayesian Information Criterion (BIC), it was selected to be compared with an even more complex model (the most complex being a cubic model). Group differences were then assessed using a log-likelihood approach. As a result, the developmental trajectories of both groups could either be not significantly different,

significantly differ regarding their intercept (i.e. one of the two groups has a higher performance on a given variable but this difference remains the same across development), or significantly differ regarding their shape (i.e. the developmental trajectory of the two groups is different).

2.2.Memory performance. To look at memory performance in relation to time of testing, repeated measures ANOVA were carried on hit rates and false alarm rates (see Table 1 below). For the hit rates, the ANOVA revealed a significant group effect ($F(1,92) = 5.93, p = .017, \eta^2 = .061$) with the control participants recognizing more words than the 22q11DS participants. A significant effect of visit was also reported ($F(1,92) = 133.89, p = .001, \eta^2 = .593$) with more words being recognized at Time 2. No significant interaction was observed ($F(1,92) = 1.29, p = .259, \eta^2 = .014$). For the false alarm rates, the ANOVA revealed only a significant effect of visit ($F(1,92) = 111.281, p = .001, \eta^2 = .547$), with more false alarms for both groups at the second visit. There was no group effect ($F(1,92) = 3.23, p = .076, \eta^2 = .034$) and no significant interaction ($F(1,92) = 1.98, p = .16, \eta^2 = .021$).

To better examine the developmental trajectory of hit rates in the two groups, mixed model regression analyses were performed as outlined above. A linear trajectory best fitted the data, and the trajectory of participants with 22q11DS was not significantly different from the trajectory of the control group (see Figure 1 below, group effect: $b = -0.23, p = 0.210$).

(Insert Figure 1)

2.3Directed Forgetting effect. Repeated measures ANOVA for directed forgetting established a significant main effect of Encoding Condition, with more TBR items correctly recognized than TBF items ($F(1,92) = 22.19, p < .001, \eta^2 = .194$). A main effect of Group was found ($F(1,92) = 11.04, p = .001, \eta^2 = .107$), with the participants with 22q11DS recognizing fewer items overall, consistent with the above analysis (see Table 1). No significant main effect of Time of

Testing was observed ($F(1,92) = .57, p = .45, \eta^2 = .006$), nor any Group x Time of Testing interaction ($F(1,92) = 2.17, p = .14, \eta^2 = .023$) or encoding condition x time of testing interaction ($F(1,92) = 1.34, p = .25, \eta^2 = .014$). The Group x Encoding Condition interaction also failed to reach significance ($F(1,92) = 3.31, p = .072, \eta^2 = .035$). Finally, the three way interaction reached significance ($F(1,92) = 6.84, p = .010, \eta^2 = .069$). As in the current literature, several means of quantifying the TBR-TBF effect exist, for completeness we report these here. The absolute DF effect (recognition of TBR minus TBF items) was not significantly different between groups ($F(1, 92) = 3.31, p = .07, \eta^2 = .035$). There was no difference between Time 1 and Time 2 for the absolute DF effect ($F(1,92) = 1.34, p = .24, \eta^2 = .014$), but there was however a significant Time x Group interaction ($F(1,92) = 6.84, p = .01, \eta^2 = .069$). The proportionate DF effect (recognition of TBR items/recognition of TBR + TBF items) did show a significant group effect ($F(1,92) = 5.25, p = .024, \eta^2 = .054$) with the 22q11.2 participants showing overall a higher directed forgetting effect. There was no effect of time ($F(1,92) = .53, p = .407, \eta^2 = .006$), and a significant interaction ($F(1,92) = 6.39, p = .013, \eta^2 = .065$).

(Insert Table 1)

Again, the developmental trajectories of TBR and TBF correctly recognized words was explored using mixed model regression analyses (see Figure 2). Regarding TBR words, a linear model best fitted the data and the shape of the trajectory was significantly different between the two groups (interaction effect: $b = 0.185, p = 0.046$). Indeed, whereas the number of TBR correctly recognized words significantly increased with age in the control group, the trajectory was more constant in the group of participants with 22q11DS. As for TBF words, a quadratic model best fitted the data and the shape of the trajectory was also significantly different between the two groups (interaction effect: $b = -2.12, p = 0.009$), with a decrease in the number of words recognized in 22Q11DS participants with age.

(Insert Figure 2)

2.4. TBF and TBR memory cues. On the proportion of TBR and TBF memory cues correctly identified, the repeated three way ANOVA showed a significant main effect of group ($F(1,88) = 12.34, p < .001, \eta^2 = .123$), with more cue errors in the 22q11DS group. The condition effect was also significant with more cue errors for the TBF items ($F(1,88) = 7.27, p = .008, \eta^2 = .076$), and the encoding condition x group interaction reached significance ($F(1,88) = 9.60, p = .003, \eta^2 = .098$). No other significant effect or interaction was found.

Again, the developmental trajectory of cue memory errors was examined using mixed model regression analyses (see Figure 3). Because the distribution of the number of cue memory errors in the TBR and TBF conditions was highly skewed, only the total number of cue memory errors was examined. A linear trajectory best fitted the data and revealed a significantly different trajectory between the two groups (interaction effect: $b = -0.24, p = 0.039$). Indeed, whereas the number of cue memory errors decreased with age in the control group, it remained relatively stable in the group of participants with 22q11DS.

(Insert Figure 3)

2.5. Comparison between 22q11DS higher than 70 IQ group and lower than 70 IQ group. In order to determine whether the cognitive profile observed in the group of 22q11DS participants is specific rather than due to a more general factor, analyses were carried out to compare memory performance (hit rates, false alarm rates, cue memory errors) between a group of 22q11DS participants with an IQ higher than 70 and a group of 22q11DS participants with an IQ lower than 70 (see Maeder et al., 2016 for a similar procedure). This procedure instead of an ANCOVA was chosen following the statistical consideration made by Adams et al. (1985). The ANOVA first revealed no group differences in hit rates ($F(1, 50) = 2.13, p = .151$). Finally, regarding the DF effect when compared to each other, the *lower than 70* group (26

participants) differed from the *higher than 70* group (25 participants) in the number of correct items recognized ($F(1, 50) = 12.01, p = .001$). However, the condition effect remains significant ($F(1,50) = 21.26, p = .001$) showing that both groups show the DF effect. Furthermore, the group difference on the number of cue memory errors remains significant ($F(1,50) = 9.25, p = .004$). Groups again were still matched for age ($t(49) = 1.30, p = .196$). The *lower than 70* group had a mean total IQ score of 61.52 ± 6.73 and the *higher than 70* group a mean total IQ score of 79.15 ± 6.73 ($t(43) = 12.08, p = .001$). To summarize, these findings confirm that general functioning as measured by the IQ does not seem to play a major role in the memory deficits observed (see Debbané et al., 2018 for similar findings).

2.6 Correlations between memory performance and brain morphology. The association between brain morphology and memory performance was investigated in the entire group of patients and analyses ran using specific region interests (ROIs) methods based on previous findings using the DF paradigm (Bastin, Feyers, Marjerus, Balteau, Degueldre et al., 2012). No significant correlations were evident between the correct TBR and TBF responses and cortical volume, thickness and surface area at T1, in both the controls and the patients with 22q11DS (all $p > 0.05$). Only one significant correlation was evident, in the group of patients, between cortical thickness in the left entorhinal cortex and the number of correct answers in the TBR condition ($p < 0.001, RHO = -0.5$). When correlating the developmental changes of brain morphology with the changes in memory performance, we found different correlations in patients and controls (Figure 4, Table 2). Significant interaction effects were evident in the posterior cingulate cortex (PCC) and the entorhinal cortex for the TBR condition and in the middle frontal cortex for the TBF condition. Specifically, cortical thinning is associated with increased number of correct answers in the TBR condition in the control group. This relationship is reversed in the patients, where reduced thickness in this region is associated to the reduced number of correct answers with age. In contrast, in the entorhinal cortex,

controls show a positive correlation between the number of correctly remembered items and cortical thickness, meaning that increased thickness is associated to increased number of correct answers with age. Again, this association is reverted in the patients with 22q11DS. These results suggest that different trajectories of cortical thickness between patients and controls influence the development of memory performance. Similarly, different associations were observed between the changes of cortical thickness in the middle frontal cortex and changes in memory performance for the TBF condition in patients and controls, with the patients showing a positive association between decreased cortical thickness and decreased number of correct answers. When a Bonferroni correction for multiple comparisons is applied, the results that remain significant are the interaction effects in the bilateral PCC ($P=0.004$).

(Insert Figure 4 and Table 2)

We further investigated if cue memory errors in the TBF condition were associated with differences in hippocampal volume. We found no significant correlation between attribution errors in the TBF condition and hippocampal volume in controls (left hippocampus, $p=0.77$, $RHO=0.05$; right hippocampus, $p=0.3$, $RHO=0.17$) and in patients (left hippocampus, $p=0.8$, $RHO=-0.038$; right hippocampus, $p=0.6$, $RHO=-0.07$) at T1.

When investigating the correlation between developmental trajectories of cortical volume in the hippocampus and cue memory errors in the TBF condition, we found different trajectories in patients and controls. In particular, the patients showed a negative correlation between reduced hippocampal volume and increased number of errors with age (Figure 5).

(Insert Figure 5)

3.Discussion

The purpose of this study was to explore developmental trajectories of intentional forgetting in 22q11.2 deletion syndrome and the brain correlates to those developmental changes. First of all, our results showed in general a poorer memory performance in participants with 22q11DS, in contrast with previous studies also using verbal materials and demonstrating that people with 22q11DS (adolescents and adults) have similar levels of performance than healthy controls (Debbané, Glaser, & Eliez, 2008; Debbané, Van der Linden, Glaser, & Eliez, 2008; Lajiness-O'Neill, Beaulieu, Titus, Asamoah, Bigler, Bawle et al., 2005; Lewandowski, Shashi, Berry, & Kwapil, 2007). Despite this lower recognition performance, we nonetheless confirmed Debbané et al.'s findings (2008) regarding a DF effect, as participants with 22Q11DS recognized more TBR than TBF items. These findings contrast with the results of several studies in clinical populations that represent frequent comorbidities in 22Q11DS carriers. Indeed, the presence of 22q11DS confers an increased risk for a range of neurodevelopmental disorders, schizophrenia in particular (Schneider, Debbané, Basset, Chow, Fung, van den Bree et al., 2014). So far, two studies have reported decreased DF effects in schizophrenia (Muller, Ullsperger, Hammerstein, Sachweh & Becker, 2005; Sonntag, Gokalsing, Olivier, Robert, Burglen, Kauffman-Muller et al., 2003).

In 22Q11DS, previous studies lead us to believe that different developmental trajectories could be observed in this clinical population. For example, developmental trajectories can be described as trajectories lacking shape, with the same general form, but with the curve shifted along the age axis or differences in the slope can be observed with spurts at one or several time points (Anderson, 2002; Anderson & Reidy, 2012; Diamond, 2013). The developmental trajectory analyses revealed that there was a steady increase in the recognition of TBR items over time in the control group, with a flatter trajectory in the 22q11DS group. The TBF items did not fit such a linear model, but followed a more complex quadratic model, but again revealed group differences. According to how the directed forgetting effect was quantified, there were differences in how it evolved over time in the two

groups. Perhaps the clearest indication of how it evolves is in the significant three way interaction simply comparing the TBR and TBF rates with time point and group. This shows that if anything, the 22Q11DS group shows differences in time according to the number of correctly recognized items in the TBR condition, which falls over time, whereas the recognition of these items improves over time in the control group. For the TBF items, in comparison, both groups correctly recognized a similar number of items at the two time points.

Several studies show that the formation of new specific personal events, rich in contextual details, improves during childhood until adolescence (e.g. Brainerd, Holliday & Reyna, 2004; Ghetti and Angelini, 2008; Howe, Courage & Rooksby, 2009). Of particular interest, many studies now suggest the existence of different developmental trajectories for the different components of episodic memory. For example, familiarity-based processes develop earlier than recollection-based ones (Billingsley, Smith & McAndrews, 2002; Ghetti and Angelini, 2008; Brainerd & Reyna, 2012). Furthermore, recalling contextual information develops later than recalling the information itself (Cycowicz, Friedman, Snodgrass & Duff, 2001; Cycowicz, Friedman & Duff, 2003; Pirogovsky, Gilbert & Murphy, 2006). Of particular interest, this study shows that control participants' ability to remember the cue associated to the items (TBR or TBF) increase with age, as the results showed a decrease in errors, therefore confirming the idea of a developmental trend on the ability to encode the type of cue associated to the target (Lehman, Morath, Franklin & Elbaz, 1998). However, unlike control participants, participants with 22q11DS did not show such a decrease in errors. These findings suggest that children with 22q11DS may have difficulties to encode the type of cue associated to each item (i.e. Remember or Forget), a process described to be central to intentional forgetting in the Directed-Forgetting paradigm (Bjork, 1972).

Inhibition in memory is an important cognitive process in everyday life as it is supposed to facilitate the learning of relevant information by keeping irrelevant information from entering and be maintained in memory. Inhibiting irrelevant information is crucial to reduce cognitive load and increase efficiency by, for example, allowing more elaborated encoding (Sahakyan and Delaney, 2005). In other words, a better inhibition leads to better memory performance. As an illustration, in the developmental literature, inhibition models have long suggested that developmental changes in cognitive inhibition account for an increase in performance, such as memory performance (Harnishfeger and Bjorklund, 1993). The fact that individuals with 22q11DS show similar DF effect to controls therefore suggests an equivalent level of inhibition. However, this does not lead to an increase in memory performance, as our findings showed that recognition performance did not increase with age. If DF can be considered as a reflection of inhibition capacities in memory, our findings might seem surprising. Indeed, some studies but not all report impairments on tasks requiring interference control (Bish, Ferrante, McDonald-McGinn, Zackai & Simon, 2005 but see Campbell, Azuma, Ambery, Stevens, Smith et al., 2010), oculomotor inhibition (Sobin et al., 2005) and inhibition of motor response measured using a Go-NoGo task (Shapiro, Wong & Simon, 2013 but see Campbell et al., 2010). Altogether, these findings might suggest a fractionation of inhibition in 22q11DS.

A major aim of this study was to determine the neural correlates of intentional forgetting in individuals with 22q11DS from a developmental perspective. One of the main finding in this study is a developmental effect on recognition performance in the patient group. In the DF paradigm, previous studies have shown that successful recognition of TBR items reveals the activation of several brain regions involved in episodic memory such as the left hippocampus, the left inferior parietal gyrus, or the posterior cingulate cortex, regions usually reported in relation to recollection processes (e.g., Dobbins, Rice, Wagner & Schacter, 2003; Spanio, Davidson, Kim, Han, Moscovith et al., 2009; Yonelinas, Otten, Shaw & Rugg,

2005). Our study confirmed the implication of those brain regions in the successful recognition of TBR items and add interesting findings regarding the developmental perspective. In particular, we showed that in patients with 22q11DS the association between the development of cortical thickness in the posterior cingulate cortex and the number of correct answers in the TBR condition is altered compared to controls. Cortical thickness is a measure that develops through adolescence and altered developmental trajectories have been observed in patients with 22q11DS (). These alterations can be due to several mechanisms such as impaired intermediate progenitor cells proliferation, altered synaptic pruning or differences in myelination. Our results suggest that the observed altered development in cortical thickness may have an impact on memory performance in patients with 22q11DS, although a casual relationship cannot be established on the basis of the correlation analysis performed in this study.

Furthermore, ERP studies have showed larger parietal late positive potentials in response to TBR items than TBF items, supporting the idea that TBR items involve increased rehearsal at encoding (Bailey & Chapman, 2012; Gallant & Dyson, 2016; Gao, Cao, Qi, Wang, Zhang & Li, 2016; Hauswald, Schulz, Iordanov, & Kissler, 2010).

fMRI studies have shown widespread activations in anterior and posterior regions in response to TBF cues. In particular, the right superior/middle frontal gyrus seems differentially activated when information is cued to be forgotten compared to when it is cued to be remembered (Nowicka et al., 2011; Wylie et al., 2008; Yang et al., 2013). Penolazzi et al. (2014) successfully abolished the DF effect by applying cathodal stimulation over the right prefrontal cortex, supporting the idea that intentional forgetting relies on the recruitment of inhibitory processes. Right prefrontal brain activity has also been implicated in inhibitory control processes (Anderson et al., 2004; Rizio & Denis, 2013). Furthermore, Bastin et al. (2012) showed activation of the dorsomedial thalamus for items to forget but nevertheless correctly recognized. The involvement of this region, associated with familiarity based

memory processes, suggests that familiarity with items might lead to errors when inhibitory processes are failing. Additionally, activity in the hippocampus was found for intentional forgetting of TBF items (Nowicka et al., 2001; Wylie et al., 2008). Regarding hippocampus activation, our study revealed a negative correlation between reduced hippocampal volume and increased number of wrongly identified TBF cues with age in the 22q11DS sample. This finding is in line with other results showing a relationship between hippocampus and source memory (Yu, Johnson & Rugg, 2012) and with the studies suggesting that brain changes in the hippocampus in 22Q11DS would explain memory problems encountered by those patients (Deboer et al., 2017; Debanné et al., 2006).

4. Conclusion

To conclude and summarize, the main findings of this longitudinal study was to show that participants with 22q11DS recognized fewer TBR items and showed a different developmental pattern in comparison to controls as they did not show an increase in recognition of TBR items with age. Furthermore, this study showed that participants with 22q11DS made more source memory errors with age and this behaviour was associated with a decline in hippocampal volume.

5. Method

5.1 Participants

Individuals with 22q11DS. 51 individuals with 22q11DS (27 females and 24 males) were recruited to this study. During the first session, they were 7 to 25 years old ($M = 13.75 \pm 4.26$). The sample had a mean total IQ score of 70.50 ± 10.75 in the first session (T1), assessed by age-appropriate Wechsler Intelligence Scale (Wechsler Intelligence Scale for Children-III, 1991). A second session (T2) was performed with the same sample approximately three years later. Participants had then a mean total IQ score of 70.03 ± 11.77 .

Typically developing individuals. The comparison group is composed of 43 typically developing individuals (24 females and 19 males), matched for age ($M = 13.50 \pm 4.91$) and gender with the VCFS group. This control group had a mean total IQ score of 111.23 ± 12.45 in the first session, and of 110.02 ± 12.03 in the second session.

Participants were recruited using advertisements in patient associations, newsletters and word-of-mouth. The presence of a 22q11.2 deletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). Written informed consent was obtained from participants and their parents (if the participant was younger than 18 years old) under protocols approved by the Geneva Ethics Committee (Switzerland- IRB number: PB-2016-01470).

5.2 Directed Forgetting task

Procedure. This task was presented on a computer screen. First, instructions appear on the screen, read at loud by the experimenter, informing participants that they will see a list of words presented one by one, and followed by a symbol giving the instruction to remember or forget the word. Participants had to remember the word (TBR-items) when a green circle appeared, and to forget the word (TBF-item) when it was a red circle. Participants were asked to read each word aloud and to pay attention to the symbol following the item. Before starting, participants repeated the meaning of each symbol in order to check if participants understood the task.

Thirty words were presented in a random order. Half the words were followed by a green circle, and the other half by a red circle. Each word appeared for 2,000 ms in black font on a white background. There was a subsequent intertrial interval of 1,000 ms. Stimuli presentation was performed by E-prime 1.0 software (Psychological Software Tools, 2002). The Brulex database (Content, Mousty & Radeau, 1990) was used to generate 60 bisyllabic words, divided into two separated lists balanced for frequency (see www.lexique.org) and

complexity (length of words from 4 to 9 letters); one list of studied words and one list of distractors. Then, the studied words were divided into two separate lists of 15 words (to be remembered or to be forgotten), balanced for frequency and complexity.

Immediately after the presentation, participants filled out a recognition test, with both the 30 studied and 30 distractor words, presented in fixed random order. Next to each word, participants were asked to say if it was old or new (studied or distractor). This procedure allowed for comparisons between correct recognition, false alarms and directed forgetting effects (DF effects). Moreover, when participants discriminated the word as old, they had to say if it was a TBR- or a TBF-item.

Participants were tested during two different sessions, with a mean interval of 3.33 years (SD=.54) between consecutive visits for the controls and 3.45 years (SD=.71) for the participants with 22q11DS (no significant difference between groups, $t(91)=.93$, $p=.35$).

5.3 Neuroimaging data acquisition and analysis. Good quality neuroimaging data were available for 47 (27 females, age=16±6.7) patients with 22q11DS and 42 (24 females, age=13.5±5 years) controls. T1-weighted images were acquired using a 1.5T Philips Intera scanner (20 patients, 26 controls) or a 3T Siemens Trio scanner (27 patients with 22q11DS, 16 controls) at the Centre of Biomedical Imaging (CIBM) in Geneva. Sequence parameters for the 1.5T machine were: 124 coronal slices, voxel size 0.94 × 0.94 × 1.5 mm, TR = 35 ms, TE = 6 ms, and flip angle = 45°; the parameters for the 3T machine were: 192 coronal slices, voxel size 0.86 × 0.86 × 1.1 mm, TR = 2500, TE = 3 ms, and flip angle = 8°. High reliability across the two scanners has been reported in a previous study (Mutlu, Schneider, Debbane, Badoud, Eliez & Schaer, 2013).

T1-weighted images were used to extract measures of brain morphology, namely cortical volume, thickness and surface area, using *Freesurfer* (<http://surfer.nmr.mgh.harvard.edu>). First, the white and pial cortical surfaces were reconstructed using an automated procedure,

visually inspected and, if necessary, corrected by experienced users. Cortical volume, thickness and surface area were then extracted from specific regions interest (ROIs) showed to be involved in the successful encoding or retrieval of items to remember or to forget (Bastin, Feyers, Marjerus, Balteau, Degueldre et al., 2012). In particular, regions involved in the TBR condition are the entorhinal, anterior medial prefrontal, superior parietal and posterior cingulate cortices, the hippocampus, and the precuneus. Regions involved in the TBF condition are instead the middle frontal and posterior parietal cortices. These ROIs were extracted from a well validated parcellation (Desikan, Segonne, Fischl, Quinn, Dickerson et al., 2006) and are displayed in Figure 5 and listed in Table 2.

In order to assess if differences in memory performance are associated with alterations in brain morphology in patients with 22q11DS, we conducted a correlation analysis between the number of correct TBR and TBF items at T1 (47 patients, 27 females, age at T1 = 16 ± 6.7); 42 controls, 24 females, age at T1 = 13.5 ± 5 years) and the brain morphological measures extracted from the correspondent ROIs in both groups. We used a Spearman correlation coefficient and included age, gender and type of scanner as covariates.

We then further wanted to investigate if different development of memory performance with age was associated with an underlying difference in the maturation of brain morphology between patients and controls. For this analysis, we selected a subgroup of participants for which neuroimaging data were available at T2 (44 patients, 25 females, age at T2= 19.2 ± 5.8 ; 36 controls, 20 females, age at T2= 17.4 ± 5.2). The correlation between changes in memory performance and changes brain morphology was conducted using a mixed model approach similar to the one described above for the analysis of cognitive data. Within-subject factors were modelled as random effects and population parameters (diagnosis and memory scores in this case) as fixed effects. Gender and type of scanner were used as covariates.

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7. Figures Legends

Figure 1: Developmental trajectory of hit rates in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

Figure 2 : Developmental trajectory of the number of TBR and TBF words correctly recognized words in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

Figure 3: Developmental trajectory of the number of cue memory errors in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

Figure 4. Graphical representation of the correlation between changes in memory scores and brain morphology. The brain maps show the ROIs implicated in the consolidation or retrieval of to be remembered (green regions) or to be forgotten (pink regions) items. The plots indicate the correlation between changes in memory scores (TBR or TBF) and changes in morphological measures (thickness or surface area) with age in the corresponding ROIs.

Figure 5. Correlation between changes in the number of cue memory errors and changes in hippocampal volume with age.

Table 1. Group performance on the Directed Forgetting Paradigm

Table 2. Results of the correlation analysis between changes in the number of correct TBR and TBF items and changes in cortical volume, thickness and surface area in the corresponding regions of interest. The significant correlations have been highlighted in bold character. Abbreviations: TBR= to be remembered, TBF= to be forgotten, lh=left, rh=right, PCC= posterior cingulate cortex.

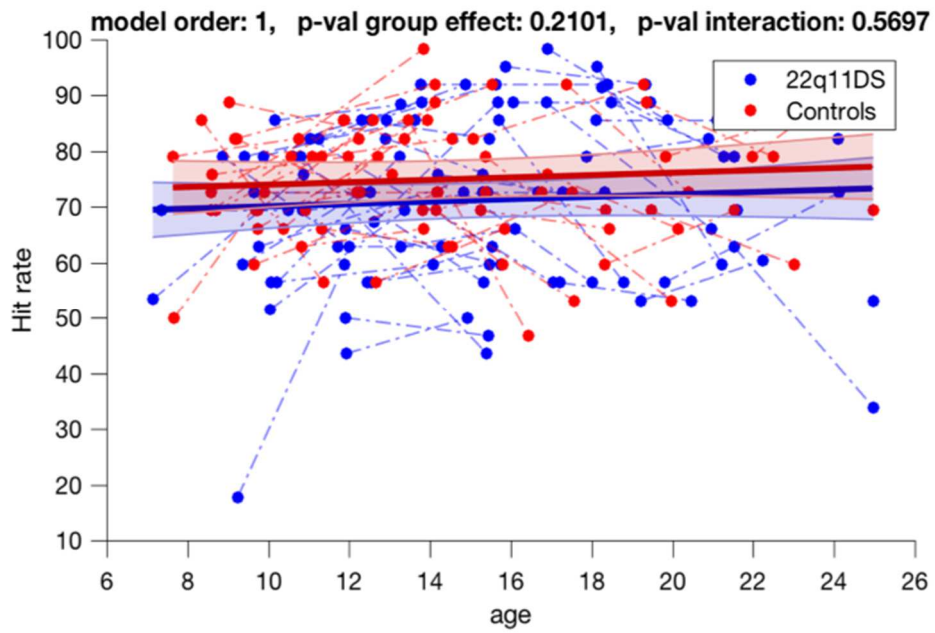


Figure 1: Developmental trajectory of hit rates in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

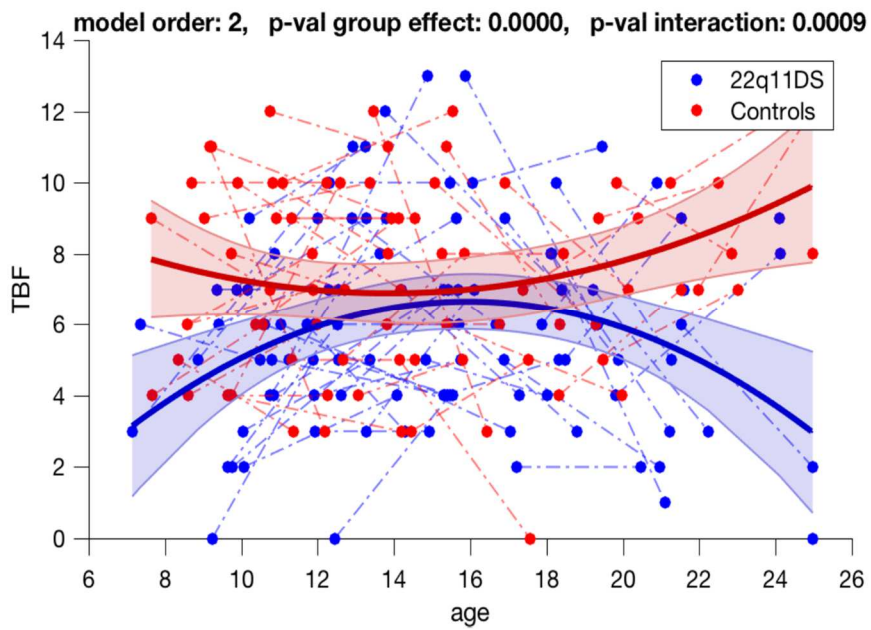
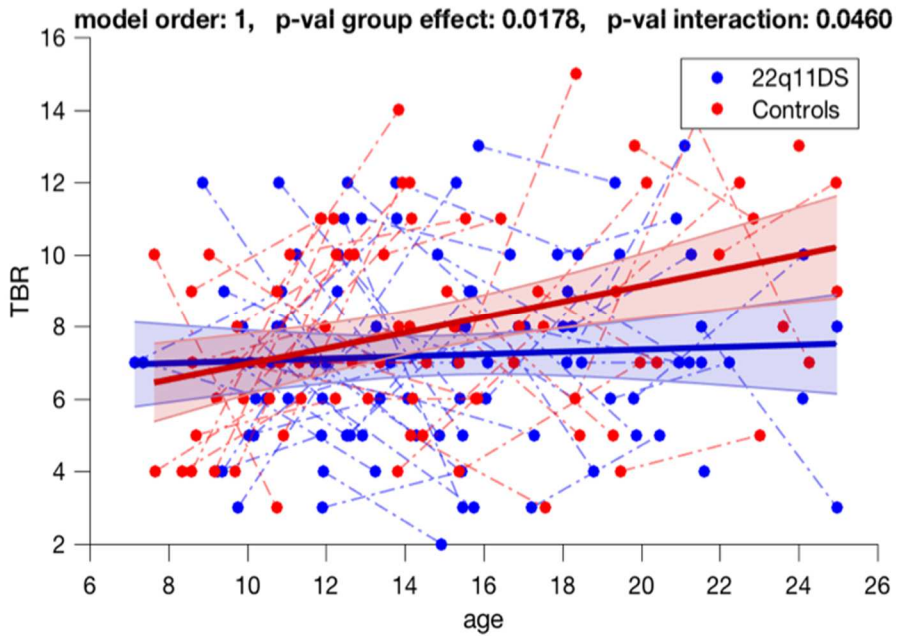


Figure 2 : Developmental trajectory of the number of TBR and TBF words correctly recognized words in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

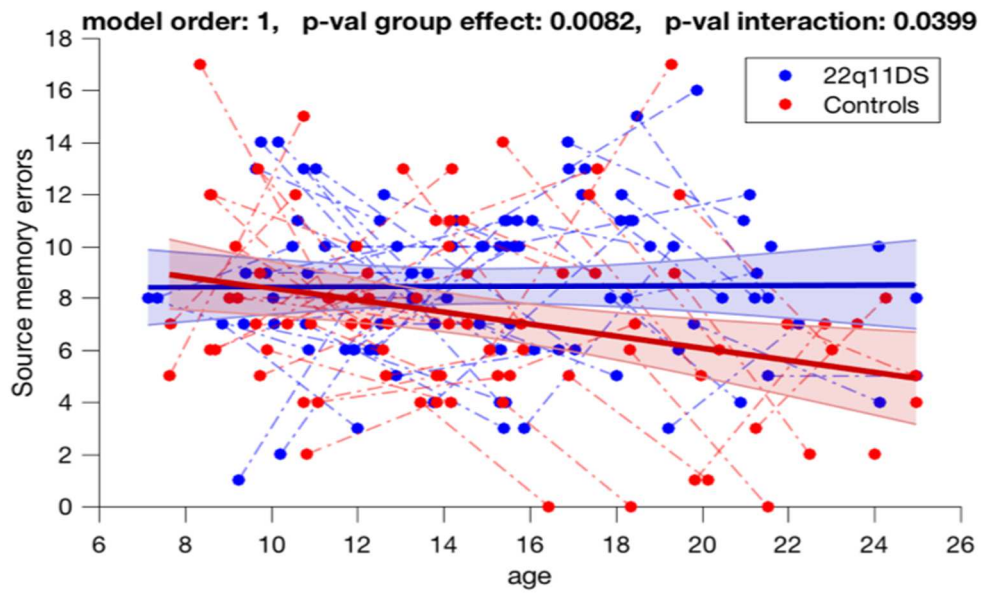


Figure 3: Developmental trajectory of the number of cue memory errors in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

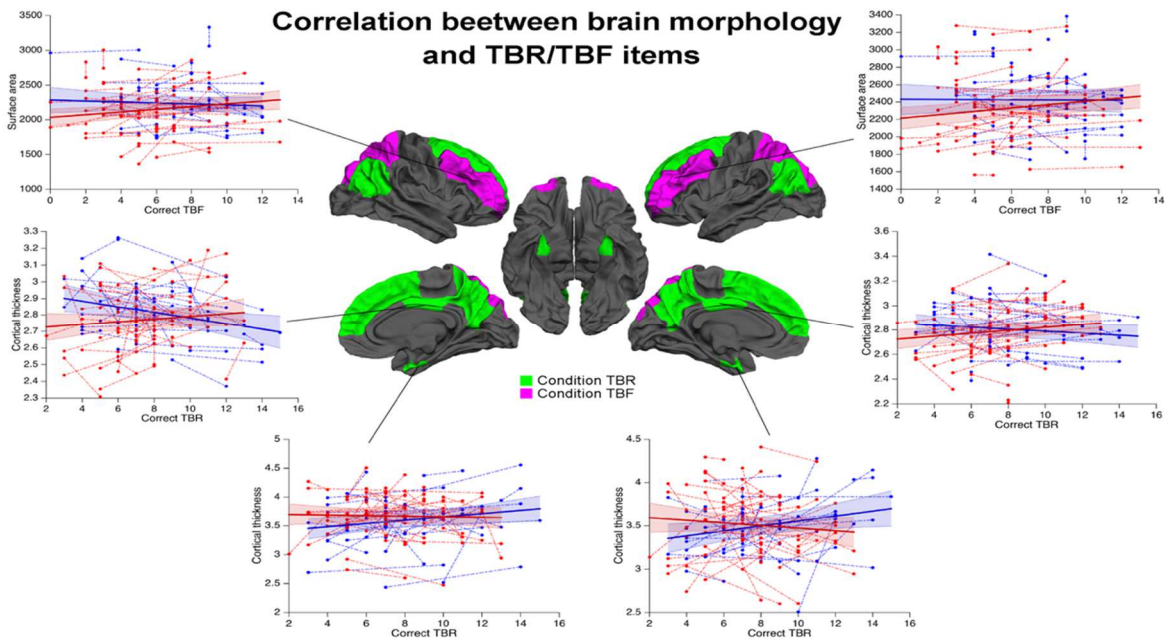


Figure 4. Graphical representation of the correlation between changes in memory scores and brain morphology. The brain maps show the ROIs implicated in the consolidation or retrieval of to be remembered (green regions) or to be forgotten (pink regions) items. The plots indicate the correlation between changes in memory scores (TBR or TBF) and changes in morphological measures (thickness or surface area) with age in the corresponding ROIs.

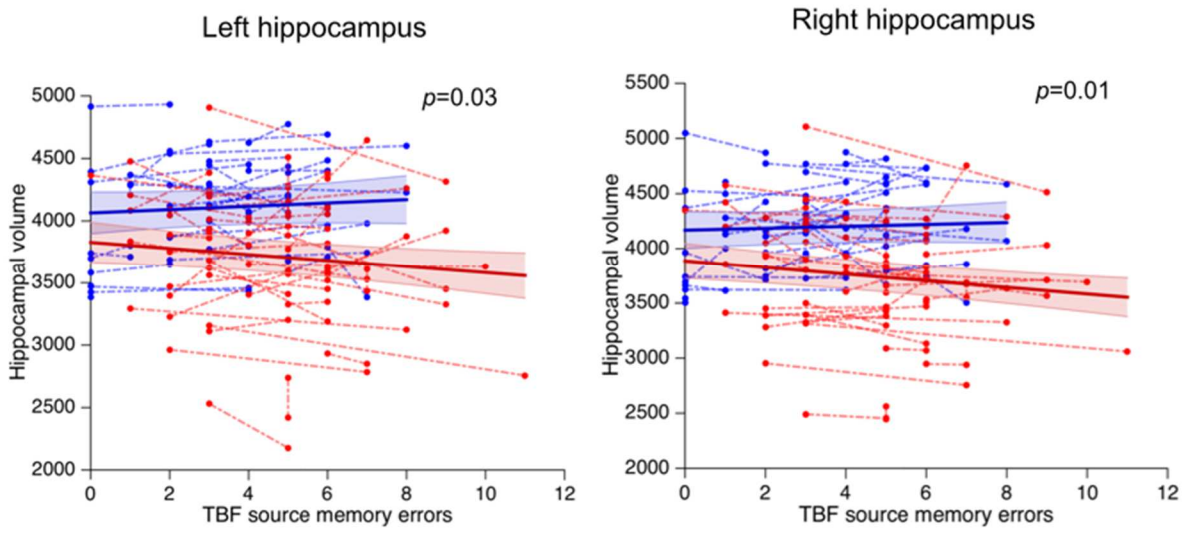


Figure 5. Correlation between changes in the number of cue memory errors and changes in hippocampal volume with age.

Table 1. Group performance on the Directed Forgetting Paradigm

| | 22q11DS participants (n=51) | | Control participants (n=43) | |
|-------------------------|--------------------------------|---------------|--------------------------------|--------------|
| | T1 | T2 | T1 | T2 |
| Hit rate | 71.74 ± 16.02 | 87.59 ± 10.02 | 74.38 ± 9.81 | 93.68 ± 6.52 |
| False Alarm rate | 9.34 ± 10.59 | 24.06 ± 9.45 | 8.29 ± 9.37 | 19.54 ± 8.51 |
| TBR hits | 7.43 ± 2.54 | 6.88 ± 2.62 | 7.32 ± 2.58 | 8.83 ± 3.05 |
| TBF hits | 5.66 ± 2.88 | 5.86 ± 2.87 | 7.67 ± 2.79 | 7.25 ± 2.70 |
| R-F | 1.76 ± 3.17 | 1.02 ± .3.50 | -.35 ± 2.76 | 1.58 ± 3.37 |
| R/F | .58 ± .15 | .54 ± .14 | .49 ± .09 | .56 ± .13 |
| TBR Source memory error | .67 ± .56 | .72 ± .59 | .72 ± .58 | .49 ± .49 |
| TBF Source memory error | 1.08 ± .79 | 1.19 ± .1.66 | .58 ± .53 | .56 ± .53 |

Note. T1 = Time 1; T2 = Time 2.

Hit rate = $((\text{hits} + 0.5) / (\text{hits} + \text{misses} + 1)) \times 100$

False alarm rate = $((\text{false alarms} + 0.5) / (\text{false alarms} + \text{correct rejection} + 1)) \times 100$

TBR hits = To-be-remembered (TBR) items correctly recognized (on a possibility of 15 items)

TBF hits = To-be-forgotten (TBF) items correctly recognized (on a possibility of 15 items)

TBR Source memory errors: proportion of source attribution errors for TBR items (n=42 for the controls, n=48 for the patients)

TBF Source memory errors: proportion of source attribution errors for TBF items (n=42 for the controls, n=48 for the patients)

Table 2. Results of the correlation analysis between changes in the number of correct TBR and TBF items and changes in cortical volume, thickness and surface area in the corresponding regions of interest. The significant correlations have been highlighted in bold character. Abbreviations: TBR= to be remembered, TBF= to be forgotten, lh=left, rh=right, PCC= posterior cingulate cortex.

| Condition TBR | Volume | Thickness | Area | Condition TBF | Volume | Thickness | Area |
|-------------------------|---------------------|---------------------|---------------------|------------------------------------|---------------------|---------------------|---------------------|
| | pval interaction | pval interaction | pval interaction | | pval interaction | pval interaction | pval interaction |
| <i>lh enthorinal</i> | 0.445 | 0.018 | 0.757 | <i>lh caudal mid. frontal</i> | 0.056 | 0.189 | 0.063 |
| <i>rh enthorinal</i> | 0.987 | 0.084 | 0.678 | <i>rh caudal mid. frontal</i> | 0.160 | 0.619 | 0.040 |
| <i>lh sup. frontal</i> | 0.965 | 0.087 | 0.295 | <i>lh rostral mid. frontal</i> | 0.252 | 0.253 | 0.053 |
| <i>rh sup. frontal</i> | 0.989 | 0.568 | 0.754 | <i>rh rostral mid. frontal</i> | 0.838 | 0.646 | 0.349 |
| <i>lh inf. parietal</i> | 0.832 | 0.179 | 0.595 | <i>lh sup. parietal</i> | 0.379 | 0.245 | 0.449 |
| <i>rh inf. parietal</i> | 0.923 | 0.251 | 0.457 | <i>rh sup. parietal</i> | 0.568 | 0.282 | 0.602 |
| <i>lh PCC</i> | 0.769 | 0.004 | 0.188 | | | | |
| <i>rh PCC</i> | 0.270 | 0.004 | 0.547 | | | | |
| <i>lh precuneus</i> | 0.752 | 0.220 | 0.891 | | | | |
| <i>rh precuneus</i> | 0.605 | 0.463 | 0.316 | | | | |
| <i>lh hippocampus</i> | 0.553 | NA | NA | | | | |
| <i>rh hippocampus</i> | 0.157 | NA | NA | | | | |