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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 ± 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 world 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, Vortsamn 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-Yeboa 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 noticable that many researchers have already combined judgments of source with memory judgments (Conway and Dewhurst, 1995; Hicks et al., 2002; Meiser and Bro¨der, 2002; Meiser and

Sattler, 2007; Perfect et al., 1996) showing for exemle that Remember responses are associated with source recall, (Humphreys et al., 2003 ; Meiser and Bro¨ der, 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. Reduce 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 (Shaer 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, Debbane,

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, Tacikpwski & Brechmann, 2011; Wylie, Foxe & Taylor, 2008). Furthermore, right prefrontal brain activity has also been implicated in inhibitory control processes (Anderson, Ochsner, Kuhl, Cooper, Robertson, Gabrielo 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 ((hits+0.5)/(hits + misses + 1)) x 100), false alarm rate ((false alarms + 0.5)/(false alarms + correct rejection + 1)) x 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 ($F(1,92) = 5.93$, $p = .017$, $\eta p^2 = .061$) with the control participants recognizing more words than the 22q11DS participants. A significant effect of visit was also reported ($F(1,92) = 133.89$, $p = .001$, $\eta p^2 = .593$) with more words being recognized at Time 2. No significant interaction was observed ($F(1,92) = 1.29$, $p = .259$, $\eta p^2 = .014$). For the false alarm rates, the ANOVA revealed only a significant effect of visit ($F(1,92) = 111.281$, $p = 001$, $\eta p^2 = .547$), with more false alarms for both groups at the second visit. There was no group effect ($F(1,92) = 3.23$, $p = .076$, $\eta p^2 = .034$) and no significant interaction ($F(1,92) = 1.98$, $p = .16$, $\eta p^2 = .021$).

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 ($F(1,92) = 22.19$, $p<.001$, $\eta p^2 = .194$). A main effect of Group was found ($F(1,92) = 11.04$, $p = .001$, $\eta p^2 = .107$), 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 ($F(1,92) = .57$, $p = .45$, $\eta p^2 = .006$), nor any Group x Time of Testing interaction ($F(1,92) = 2.17$, $p = .14$, $\eta p^2 = .023$) or encoding condition x time of testing interaction ($F(1,92) = 1.34$, $p = .25$, $\eta p^2 = .014$). The Group x Encoding Condition interaction also failed to reach significance ($F(1,92) = 3.31$, $p = .072$, $\eta p^2 = .035$). Finally, the three way interaction reached significance ($F(1,92) = 6.84$, $p = .010$, $\eta p^2 = .069$). 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 ($F(1, 92)=3.31$, $p=.07$, $\eta p^2 = .035$). There was no difference between Time 1 and Time 2 for the absolute DF effect ($F(1,92) = 1.34$, $p = .24$, $\eta p^2 = .014$), but there was however a significant Time x Group interaction ($F(1,92) = 6.84$, $p = .01$, $\eta p^2 = .069$). The proportionate DF effect (recognition of TBR items/recognition of TBR + TBF items) did show a significant group effect ($F(1,92)= 5.25$, $p=.024$, $\eta p^2 = .054$) with the 22q11.2 participants showing overall a higher directed forgetting effect. There was no effect of time ($F(1,92)=.53$, $p=.407$, $\eta p^2 = .006$), and a significant interaction ($F(1,92)=.6.39$, $p=.913$, $\eta p^2 = .065$).

(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 TBR memory cues correctly identified, the repeated three way ANOVA showed a significant main effect of group (F(1,88) =12.34, p<.001, ηp^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, ηp^2 = .076), and the encoding condition x group interaction reached significance (F(1,88) = 9.60, p = .003, ηp^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, Debbane, 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

5.1Participants

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 ± 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 ± 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).

5.2Directed 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 Spearmann 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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6. References

Adams, K, Gregory G. Brown, G. & Grant, I. (1985) Analysis of covariance as a remedy for demographic mismatch of research subject groups: Some sobering simulations, *Journal of Clinical and Experimental Neuropsychology*, 7:4, 445-462, DOI: 10.1080/01688638508401276

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology, 8(2),* 71-82

Anderson MC, Ochsner KN, Kuhl B, Cooper J, Robertson E, Gabrieli SW, Glover GH & Gabrieli JD. (2004) Neural systems underlying the suppression of unwanted memories. *Science*. *Jan 9;303*(5655):232-5. doi: 10.1126/science.1089504. PMID: 14716015.

Anderson, P. & Reidy, N. (2012). Assessing executive function in pre-schoolers. *Neuropsychological Review, 22(4),* 345-60

Basden, B.H., & Basden, D.R. (1996). Directed forgetting: Further comparisons of the item and list methods. *Memory, 4(6),* 633-653

Bastin C, Feyers D, Majerus S, Balteau E, Degueldre C, et al. (2012) The Neural Substrates of Memory Suppression: A fMRI Exploration of Directed Forgetting. PLOS ONE 7(1): e29905. https://doi.org/10.1371/journal.pone.0029905

Bailey K, & Chapman P. (2012) When can we choose to forget? An ERP study into item-method directed forgetting of emotional words. *Brain and Cognition*. *Mar;78(2)*:133-47. doi: 10.1016/j.bandc.2011.11.004. Epub 2012 Jan 11. PMID: 22240487.

Bray NW, Turner LA, & Hersh RE. (1985) Developmental progressions and regressions in the selective remembering strategies of EMR individuals. *Am J Ment Defic*, *Sep;90(2):*198-205. PMID: 4050879.

Bilingsley, R.L., Smith, M.L., & McAndrews, M.P. (2002). Developmental patterns in priming and familiarity in explicit recollection. *Journal of Experimental Child Psychology, 82,* 251-277.

Bish, J., Ferrante, S., McDonald-McGinn, D., Zackai.E., & Simon, T., (2005). Maladaptive conflict monitoring as evidence for executive dysfunction in children with chromosome 22q11.2 deletion syndrome. *Developmental Science, 8,* 36-43 **https://doi.org/10.1111/j.1467-7687.2005.00391.x**

Biswas, A. B., & Furniss, F. (2016). Cognitive phenotype and psychiatric disorder in 22q11.2 deletion syndrome: A review. *Research in Developmental Disabilities, 53-54*, 242-257. doi: 10.1016/j.ridd.2016.02.010

Bjork, R.A. (1972). *Theoretical implications of directed forgetting.* Washington, DC: Winston

Bjork, R.A. (1989). Retrieval inhibition as an adaptative mechanism in human memory. In : Roediger, HL., III, Craik, FIM, editors. Varieties of memory and consciousness: Essays in honour of Endel Tulving. Hillsdale, NJ, England: Lawurence Erlbaum Associates, Inc.; p.309-330

Bostelmann, M., Schneider, M., Padula, M. C., Maeder, J., Schaer, M., Scariati, E., . . . Eliez, S. (2016). Visual memory profile in 22q11.2 microdeletion syndrome: are there differences in performance and neurobiological substrates between tasks linked to ventral and dorsal visual brain structures? A cross-sectional and longitudinal study. *Journal of Neurodevelopmental Disorders, 8*, 41. doi: 10.1186/s11689-016-9174-5

Brainerd, C.J., Holliday, R.E., & Reyna, V.F. (2004). Behavioral measurement of remembering phenomenologies : So simple a child can do it. *Child Development, 75,* 505-522.

Brainerd, C.J. & Reyna, V. (2012). Reliability of Children's Testimony in the Era of Developmental Reversals. *Developmental review* : DR. 32. 224-267. 10.1016/j.dr.2012.06.008.

Campbell, L. E., Azuma, R., Ambery, F., Stevens, A., Smith, A., Morris, R. G., . . . Murphy, K. C. (2010). Executive functions and memory abilities in children with 22q11.2 deletion syndrome. *Australian & New Zealand Journal of Psychiatry, 44*(4), 364-371. doi: 10.3109/00048670903489882

Campbell L, Swillen A. (2005) The cognitive spectrum in velo-cardio-facial syndrome. In: Murphy KC, Scambler PJ, editors. Velo-cardio-facial syndrome. Cambridge, MA: Cambridge University Press. pp. 147–164

Conners, CK.,S & taff, MSH (2000) Conner's continous performance test II: Computer program for windows technical guide and software manual. North Tonawanda: Multi-Health System

Content, A., Mousty, P., & Radeau, M. (1990). BRULEX. Une base de données lexicales informatisée pour le français écrit et parlé [BRULEX: A computerized lexical data base for the French language]. *L'Année Psychologique, 90*(4), 551–566. https://doi.org/10.3406/psy.1990.29428

Conway, MA. and Dewhurst, SA. Remembering, familiarity, and source monitoring. *Quarterly Journal of Experimental Psychology Section A: Human Experimental Psychology*, 48(1): 125e140, 1995.

Cycowicz YM, Friedman D, Snodgrass JG, & Duff M. (2001) Recognition and source memory for pictures in children and adults. *Neuropsychologia*, 39(3):255-67. doi: 10.1016/s0028-3932(00)00108-1. PMID: 11163604.

Cycowicz, Y., Friedman, D., & Duff, . (2003). Pictures and Their Colors: What Do Children Remember?. *Journal of cognitive neuroscience*, *15*. 759-68. 10.1162/089892903322307465.

Debbané, M., Glaser, B., & Eliez, S. (2008). Encoding and retrieval processes in velo-cardio-facial syndrome (VCFS). *Neuropsychology, 22*(2), 226-234. doi: 10.1037/0894-4105.22.2.226

Debbané, M., Glaser, B., David, M. K., Feinstein, C., & Eliez, S. (2006). Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: Neuropsychological and behavioral implications. *Schizophrenia Research, 84*(2-3), 187-193. doi: 10.1016/j.schres.2006.01.019

Debbané M, Schaer M, Farhoumand R, Glaser B, Eliez S. Hippocampal volume reduction in 22q11.2 deletion syndrome. Neuropsychologia. 2006;44(12):2360-5. doi: 10.1016/j.neuropsychologia.2006.05.006. Epub 2006 Jun 19. PMID: 16787654.

Debbané, M., Van der Linden, M., Glaser, B., & Eliez, S. (2008). Source monitoring for actions in adolescents with 22q11.2 deletion syndrome (22q11DS). *Psychological Medicine, 38*(6), 811-820. doi: 10.1017/S003329170700222X

Deboer, T., Wu, Z., Lee, A., & Simon, T. J. (2007). Hippocampal volume reduction in children with chromosome 22q11.2 deletion syndrome is associated with cognitive impairment. *Behavioral and Brain Functions, 3*, 54. doi: 10.1186/1744-9081-3-54

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, Jul 1;31(3):*968-80. doi: 10.1016/j.neuroimage.2006.01.021. Epub 2006 Mar 10. PMID: 16530430.

Diamond, A. (2013) Executive functions. *Annual Review of Psychology, 64,* 135-68

Dobbins IG, Rice HJ, Wagner AD, Schacter DL. (2003) Memory orientation and success: separable neurocognitive components underlying episodic recognition. *Neuropsychologia, 41(3):*318-33. doi: 10.1016/s0028-3932(02)00164-1. PMID: 12457757.

Flahault, A., Schaer, M., Ottet, M. C., Debbané, M., & Eliez, S. (2012). Hippocampal volume reduction in chromosome 22q11.2 deletion syndrome (22q11.2DS): a longitudinal study of morphometry and symptomatology. *Psychiatry Research, 203*(1), 1-5. doi: 10.1016/j.pscychresns.2011.09.003

Gallant, S. & Dyson, B. (2016). Neural Modulation of Directed Forgetting by Valence and Arousal: An Event-Related Potential Study. *Brain Research, 1648*. 306-316. 10.1016/j.brainres.2016.08.009.

Gao. H., Cao. B., Qi., M., Wang, J., Zhang, Q., & Li., F. (2016). Two stages of directed forgetting: Electrophysiological evidence from a short-term memory task. *Psychophysiology,* Jun;53(6):806-13. doi: 10.1111/psyp. 12628

Ghetti, S., & Angelini, L. (2008). The development of recollection and familiarity in childhood and adolescence: Evidence from the dual-process signal detection model. *Child Development, 79,* 339-358

Gothelf, D., Eliez, S., Thompson, T., Hinard, C., Penniman, L., Feinstein, C., Kwon Jin., Jo B., Antonarakis, SE., Morris, MA., & Reiss. AL. (2005). COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nature Neuroscience, 8,* 1500-1502

Grati FR, Molina Gomes D, Ferreira JC, Dupont C, Alesi V, Gouas L, Horelli-Kuitunen N, Choy KW, García-Herrero S, de la Vega AG, Piotrowski K, Genesio R, Queipo G, Malvestiti B, Hervé B, Benzacken B, Novelli A, Vago P, Piippo K, Leung TY, Maggi F, Quibel T, Tabet AC, Simoni G, Vialard F. (2015) Prevalence of recurrent pathogenic microdeletions and

microduplications in over 9500 pregnancies. *Prenat Diagn. Aug;35*(8):801-9. doi: 10.1002/pd.4613. Epub 2015 Jun 24. PMID: 25962607.

Green, T., Gothelf. D., Glaser, B., Debbane, M., Frisch, A., Kotler, M., Weizman, A., & Eliez, S. (2009). Psychiatric disorders and intellectual functioning throughout development in velo-cardiofacial (22q11.2 Deletion) Syndrome. *Journal of American Academic Child Psychiatry, 48,* 1060-1068

Harnishfeger, K. & Bjorklund, D. (1993). The ontogeny of inhibitory mechanisms: A renewed approach to cognitive development. *Emerging Themes in Cognitive Development*. 28-49.

Hauswald A, Schulz H, Iordanov T, & Kissler J. (2011) ERP dynamics underlying successful directed forgetting of neutral but not negative pictures. *Social Cogniton and Affective Neuroscience.*Sep;6(4):450-9. doi: 10.1093/scan/nsq061. Epub 2010 Jul 2. PMID: 20601423; PMCID: PMC3150854.

Hicks JL, Marsh RL, and Ritschel L. The role of recollection and partial information in source monitoring. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 28(3): 503e508, 2002.

Howe, M.L., Courage, M.L., & Rooksby, M. (2009). The genesis and development of autobiographical memory. In M.L. Courage & N. Cowan (Eds.), *The development of memory in infancy and childhood* (pp.177-196). Hove, UK: Psychology Press

Humphreys, MS., Dennis, S., Maguire, A., Reynolds, K., Bolland, SW., and Hughes, JD. What you get out of memory depends on the question you ask. *Journal of Experimental Psychology: Learning, Memory and Cognition*, 29: 797e812, 2003.

Meiser, T. and Sattler, C. Boundaries of the relation between conscious recollection and source memory for perceptual details. *Consciousness and Cognition*, 16(1): 210, 2007.

Mutlu, Schneider, Debbané, Badoud, Eliez, & Schaer (2013). Sex differences in thickness and folding developments throught the cortex. *Neuroimage, 82,* 200-207 http://dx.doi.org/10.1016/j.neuroimage.2013.05.076

Harnishfeger K. and Pope S. (1996) Intending to Forget: The Development of Cognitive Inhibition in Directed Forgetting. *Journal of Experimental Child Psychology, 62,* 292-315

Johnson HM. (1994). Processes of successful intentional forgetting. *Psychological Bulleting, 116,* 274-292

Kates, W. R., Miller, A. M., Abdulsabur, N., Antshel, K. M., Conchelos, J., Fremont, W., & Roizen, N. (2006). Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(5), 587-595. doi: 10.1097/01.chi.0000205704.33077.4a

Kates WR, Antshel KM, Faraone SV, Fremont WP, Higgins AM, Shprintzen RJ, et al. (2011) Neuroanatomic Predictors to Prodromal Psychosis in Velocardiofacial Syndrome (22q11.2 Deletion Syndrome): A Longitudinal Study. *Biol Psychiatry*. May 15;69(10):945–52.

Karayiorgou, M., Simon, T. J., & Gogos, J. A. (2010). 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nature Reviews Neuroscience, 11*(6), 402-416. doi: 10.1038/nrn2841

Lajiness-O'Neill, R., Beaulieu, I., Titus, J., Asamoah, A., Bigler, E., Bawle, E. & Pollack, R. (2005). Memory and Learning in Children with 22q11.2 Deletion Syndrome: Evidence for Ventral and Dorsal Stream Disruption?. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence*. 11. 55-71. 10.1080/09297040590911202.

Laroi, F., Collignon, O., & Van der Linden, M. (2005). Source monitoring for actions in hallucination proneness. *Cognitive Neuropsychiatry, 10,* 105-123

Lehaman, EB., Morath, R., Franklin, K., & Elbaz, V. (1998). Knowing what to remember and forget: a developmental study of cue memory in intentional forgetting. *Memory and Cognition, 26(5),* 860-8

Lewandowski KE, Shashi V, Berry PM, Kwapil TR. (2007) Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome. *Am J Med Genet B Neuropsychiatr Genet*, *Jan 5;144B(1)*:27-36. doi: 10.1002/ajmg.b.30379. PMID: 17034021.

MacLeod CM. (1998). Directed forgetting. In : Golding JM., MacLeod CM. (Eds) Intentional Forgetting : Interdisciplinary Approaches. Lawrence Earlbaum, Mahwah, pp 1-57

Maeder, J., Schneider, M., Bostelmann, M., Debbané, M., Glaser, B., Menghetti, S., . . . Eliez, S. (2016). Developmental trajectories of executive functions in 22q11.2 deletion syndrome. *Journal of Neurodevelopmental Disorders, 8*, 10. doi: 10.1186/s11689-016-9141-1

Mancini V, Sandini C, Padula MC, Zöller D, Schneider M, Schaer M, & Eliez S. (2020) Positive psychotic symptoms are associated with divergent developmental trajectories of hippocampal volume during late adolescence in patients with 22q11DS. *Molecular Psychiatry*, Nov;25(11):2844-2859. doi: 10.1038/s41380-019-0443-z. Epub 2019 Jun 4. PMID: 31164700.

Meyer, B., Gardiner, J., & Bowler, D. (2014). Directed Forgetting in High-Functioning Adults with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 44,* 2514-2524, https://doi.org/10.1007/s10803-014-2121-y

McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, Zackai EH, Emanuel BS, Vermeesch JR, Morrow BE, Scambler PJ, & Bassett AS. (2015) 22q11.2 deletion syndrome. *Nat Rev Dis Primers*, Nov 19;1:15071. doi: 10.1038/nrdp.2015.71. PMID: 27189754; PMCID: PMC4900471.

Moberg PJ, Richman MJ, Roalf DR, Morse CL, Graefe AC, Brennan L, Vickers K, Tsering W, Kamath V, Turetsky BI, Gur RC, & Gur RE. (2018) Neurocognitive Functioning in Patients with 22q11.2 Deletion Syndrome: A Meta-Analytic Review. *Behavioural Genetics*, Jul;48(4):259-270. doi: 10.1007/s10519-018-9903-5. Epub 2018 Jun 19. PMID: 29922984; PMCID: PMC7391171.

Müller, U., Ullsperger, M., Hammerstein, E., Sachweh, S. & Becker, T. (2005). Directed forgetting in schizophrenia. Prefrontal memory and inhibition deficits. *Eur Arch Psychiatry Clin Neurosci, 255*, 251-257.

Nowicka. A., Marchewka, A., Jednorog, K., Tacikowski, P., Brechmann, A. (2011). Forgetting of emotional information is hard: an fMRI study of directed forgetting. *Cerebral Cortex, 21,* 539-549. doi: 10.1093/cercor/ bhq117

Oskarsdóttir S, Vujic M, & Fasth A. (2004). Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. *Arch Dis Child.*, Feb;89(2):148-51. doi: 10.1136/adc.2003.026880. PMID: 14736631; PMCID: PMC1719787.

Penolazzi B, Stramaccia DF, Braga M, Mondini S, & Galfano G. (2014). Human memory retrieval and inhibitory control in the brain: beyond correlational evidence. *Journal of Neuroscience, May* 7;34(19):6606-10. doi: 10.1523/JNEUROSCI.0349-14.2014. PMID: 24806685; PMCID: PMC6608142.

Perfect, TJ., Mayes, AR., Downes, JJ., and Van Eijk, R. Does context discriminate recollection from familiarity in recognition memory? *Quarterly Journal of Experimental Psychology Section A: Human Experimental Psychology*, 49(3): 797e813, 1996.

Pirogovsky, T., Gilbert, P. & Murphy, C. (2006). Source and Item Memory for Odors and Objects in Children and Young Adults. *Developmental neuropsychology*. 30. 739-52. 10.1207/s15326942dn3002_5.

Radoeva PD, Bansal R, Antshel KM, Fremont W, Peterson BS, Kates WR. (2017). Longitudinal study of cerebral surface morphology in youth with 22q11.2 deletion syndrome, and association with positive symptoms of psychosis. *Journal of Child Psychology and Psychiatry, Mar;58(3):*305-314. doi: 10.1111/jcpp.12657. Epub 2016 Oct 27. PMID: 27786353; PMCID: PMC5340081.

Rizio AA, & Dennis NA. (2013). The neural correlates of cognitive control: successful remembering and intentional forgetting. *Journal of Cognitive Neuroscience, Feb;25(2)*:297-312. doi: 10.1162/jocn_a_00310. Epub 2012 Oct 15. PMID: 23066730.

Rizio A. & Dennis N.(2017) Recollection after inhibition: The effects of intentional forgetting on the neural correlates of retrieval, *Cognitive Neuroscience*, 8:1, 1-8, DOI: 10.1080/17588928.2016.1154522

Sahakyan, L., & Delaney, PF. (2005). Directed forgetting in incidental learning and recognition testing: Support for a two factor account. *Journal of Experimental Psychology: Learning, Memory & Cognition, 31(4),* 789-801 https://doi.org/10.1037/0278-7393.31.4.789

Schaer, M., Debbane, M., Bach Cuadra, M. Ottet, M., Glaser, B., Thiran, J.P., et al. (2009). Deviant trajectories of cortical maturation in 22q11.2 deletion syndrome (22q11DS): a cross-sectional and longitudinal study. *Schizophrenia Research, 115 (2-3),* 182-190 DOI: 10.1016/j.schres.2009.09.016

Schneider, M., Debbane, M., Bassett, A. S., Chow, E. W., Fung, W. L., van den Bree, M., . . . Behavior in 22q11.2 Deletion, S. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *The American Journal of Psychiatry, 171*(6), 627-639. doi: 10.1176/appi.ajp.2013.13070864

Scariati, E., Schaer, M., Karahanoglu, F., Schneider, M., & Richiardi, J. & Debbané, M. & Van De Ville, D. & Eliez, S. (2016). Large-scale functional network reorganization in 22q11.2 deletion syndrome revealed by modularity analysis. *Cortex. 82*. 10.1016/j.cortex.2016.06.004.

Shapiro, H.M., Wong, L.M., & Simon, T.J. (2013). A cross-sectional analysis of the development of response inhibition in children with chromosome 22q11.2 deletion syndrome. *Frontiers in Psychiatry, 4,* 1-10

Shprintzen, R. (2005) Velo-Cardio-Facial Syndrime: 30 Years of study. *Developmental disabilities research reviews, 14(1),* 3-10

Sobin, C., Kiley-Brabeck, K., Daniels, S., Blundell, M., Anyane-Yeboa, K., & Karayiorgou, M. (2004). Networks of attention in children with the 22q11 deletion syndrome. *Developmental Neuropsychology, 26*(2), 611-626. doi: 10.1207/s15326942dn2602_5

Sobin, C., Kiley-Brabeck, K., & Karayiorgou, M. (2005). Associations between prepulse inhibition and executive visual attention in children with the 22q11 deletion syndrome. *Molecular Psychiatry, 10*(6), 553-562. doi: 10.1038/sj.mp.4001609

Sonntag, P., Gokalsing, E., Olivier, C., Robert, P., Burglen, F., Kauffman-Muller, F., Huron, C., Salame, P., & Danion, J-M. (2003). Impaired strategic regulation of contents of conscious awareness in schizophrenia. *Consciouness and Cognition, 12,* 190-200

Souchay, C., Wojcik, D.Z., Williams, H.L., Crathern, S., & Clarke, P. (2013). Recollection in adolescents with Autism Spectrum Disorder. *Cortex*. 49(6) : 1598-609

Spaniol J, Davidson PS, Kim AS, Han H, Moscovitch M, & Grady CL. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia. Jul;47(8-9):*1765-79. doi: 10.1016/j.neuropsychologia.2009.02.028. Epub 2009 Mar 4. PMID: 19428409.

Stroop JR (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology,* 18, 643-662

Sun D, Ching CRK, Lin A, Forsyth JK, Kushan L, Vajdi A, et al. (2018) Large-scale mapping of cortical alterations in 22q11.2 deletion syndrome: Convergence with idiopathic psychosis and effects of deletion size. *Mol Psychiatry*. Jun 13;1–13.

Todor, I. (2012). Age-Related Differences in Directed Forgetting. *Procedia-Social and Behavioral Sciences, 69,* 1402-1409.

Thompson, Hallmayer, O'Hara, and Initiative AND (2011). Design considerations for characterizing psychiatric trajectories across the lifespan: application to effects of apoe-E4 on cortical thickness in alzheimer's disease.

Wong, L. M., Riggins, T., Harvey, D., Cabaral, M., & Simon, T. J. (2014). Children with chromosome 22q11.2 deletion syndrome exhibit impaired spatial working memory. *American Journal on Intellectual and Developmental Disabilities, 119*(2), 115-132. doi: 10.1352/1944-7558-119.2.115

Woodin, M., Wang, P. P., Aleman, D., McDonald-McGinn, D., Zackai, E., & Moss, E. (2001). Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. *Genetics in Medicine, 3*(1), 34-39. doi: 10.109700125817-200101000-00008

Wylie, G.R., Foxe, J.J, Taylor, T.L. (2008). Forgetting as an active process: an fMRI investigation of item-method-directed forgetting. *Cerebral Cortex, 18,* 670-682. DOI: 10.1093/cercor/bhm101

Vorstman JA, Breetvelt EJ, Duijff SN, Eliez S, Schneider M, Jalbrzikowski M, Armando M, Vicari S, Shashi V, Hooper SR, Chow EW, Fung WL, Butcher NJ, Young DA, McDonald-McGinn DM, Vogels A, van Amelsvoort T, Gothelf D, Weinberger R, Weizman A, Klaassen PW, Koops S, Kates WR, Antshel KM, Simon TJ, Ousley OY, Swillen A, Gur RE, Bearden CE, Kahn RS, & Bassett AS. (2015). International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry*, *Apr;72(4):*377-85. doi: 10.1001/jamapsychiatry.2014.2671. PMID: 25715178; PMCID: PMC4383767.

Wechsler, D. (1991). *Weschler Intelligence Scale for Children: Third Edition manual*. San Antonio, TX: The Psychological Corporation.

Yang., W., Liu, P., Xiao X., Li, X., Zeng, C., Qiu, J., & Zhang, G. (2011). Different neural substrates underlying directed forgetting for negative and neutral images: An event-related potentiel study. *Brain Research, 1441*, 53-63 Doi: 10.1016/j.brainres.2011.10.042

Yonelinas AP, Otten LJ, Shaw KN, & Rugg MD. (2005) Separating the brain regions involved in recollection and familiarity in recognition memory. *Journal of Neuroscience, Mar 16;25(11)*:3002-8. doi: 10.1523/JNEUROSCI.5295-04.2005. PMID: 15772360; PMCID: PMC6725129.

Yu, S., Johnson, J. & Rugg, M. (2012). Hippocampal activity during recognition memory co-varies with the accuracy and confidence of source memory judgments. Hippocampus. 22. 1429-37. 10.1002/hipo.20982.

Zacks, R. & Hasher, Lynn. (1994). Directed ignoring: Inhibitory regulation of working memory. Inhibitory Mechanisms in Attention, *Memory, and Language. 22*.

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.

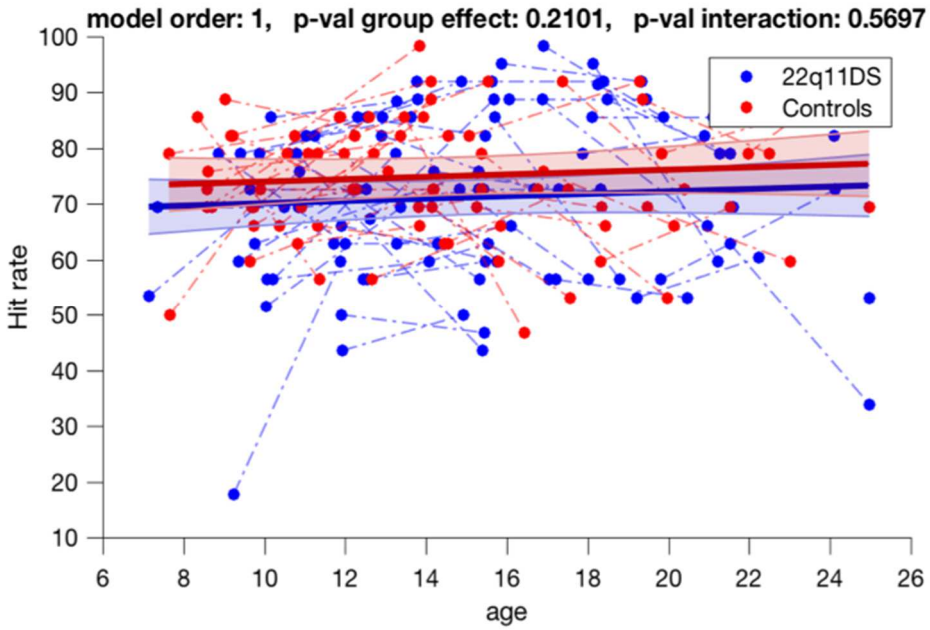
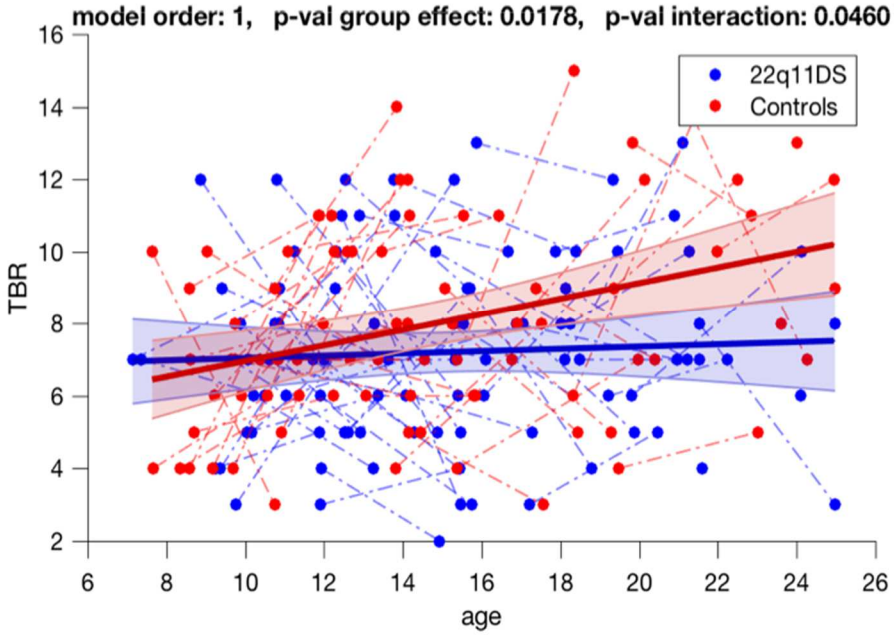


Figure 1: Developmental trajectory of hit rates in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.



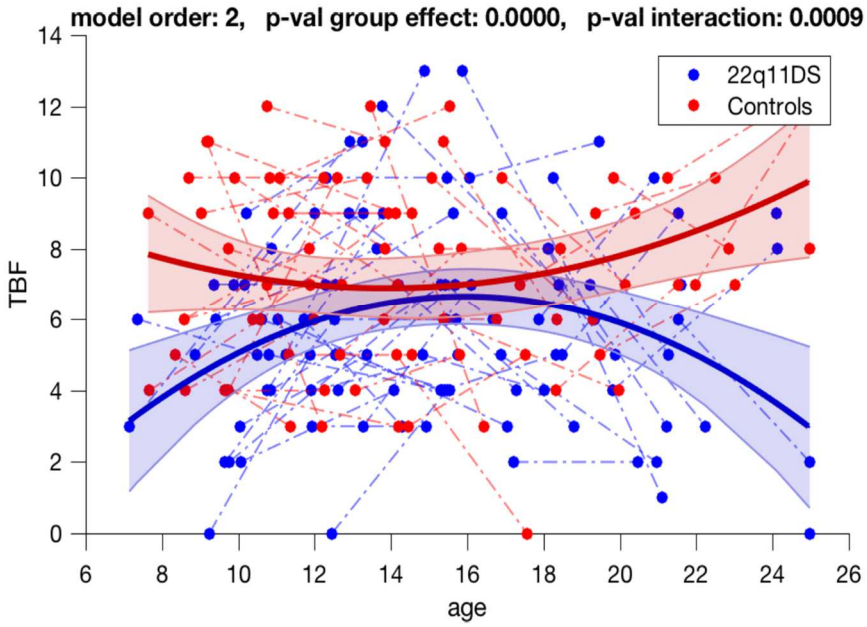


Figure 2 : Developmental trajectory of the number of TBR and TBF words correctly recognized words in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

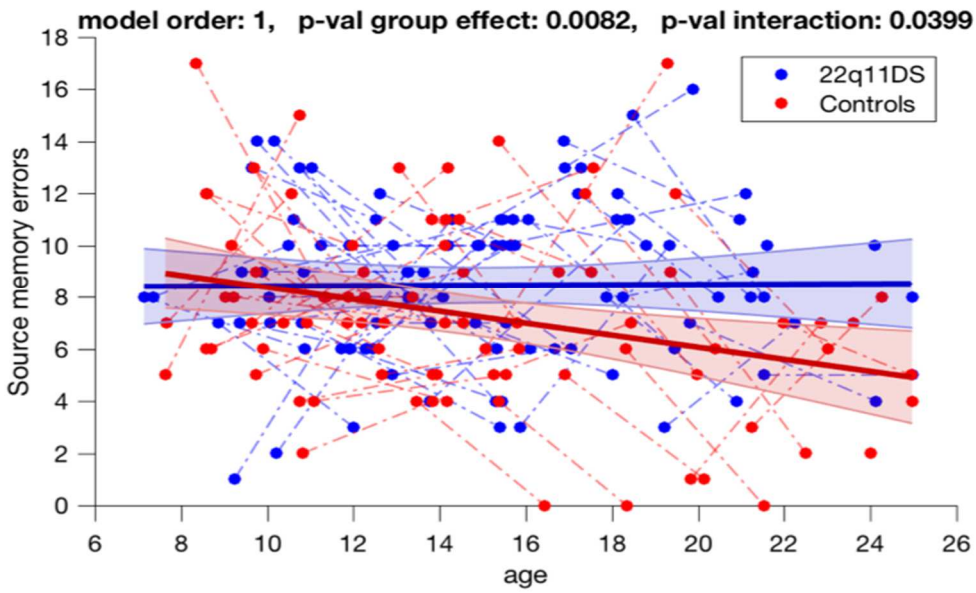


Figure 3: Developmental trajectory of the number of cue memory errors in participants with 22q11DS and healthy controls. The data points from a single participant are connected by a dotted line. The solid lines show the model fitted.

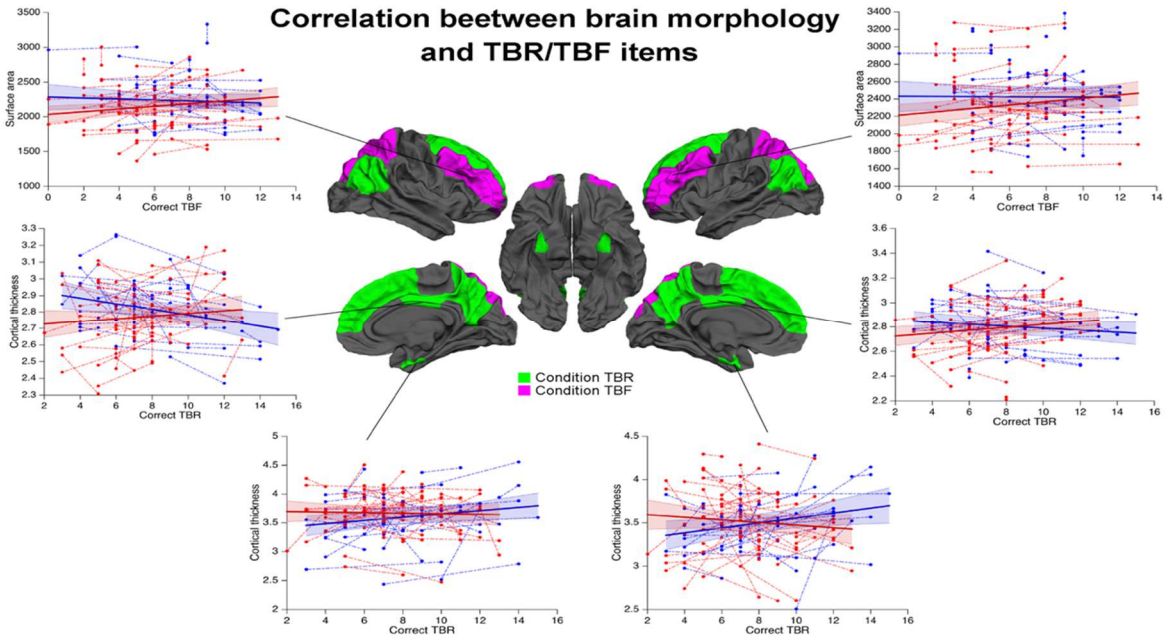


Figure 4. Graphical representation of the correlation between changes in memory scores and brain morphology. The brain maps show the ROIs implicated in the consolidation or retrieval of to be remembered (green regions) or to be forgotten (pink regions) items. The plots indicate the correlation between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

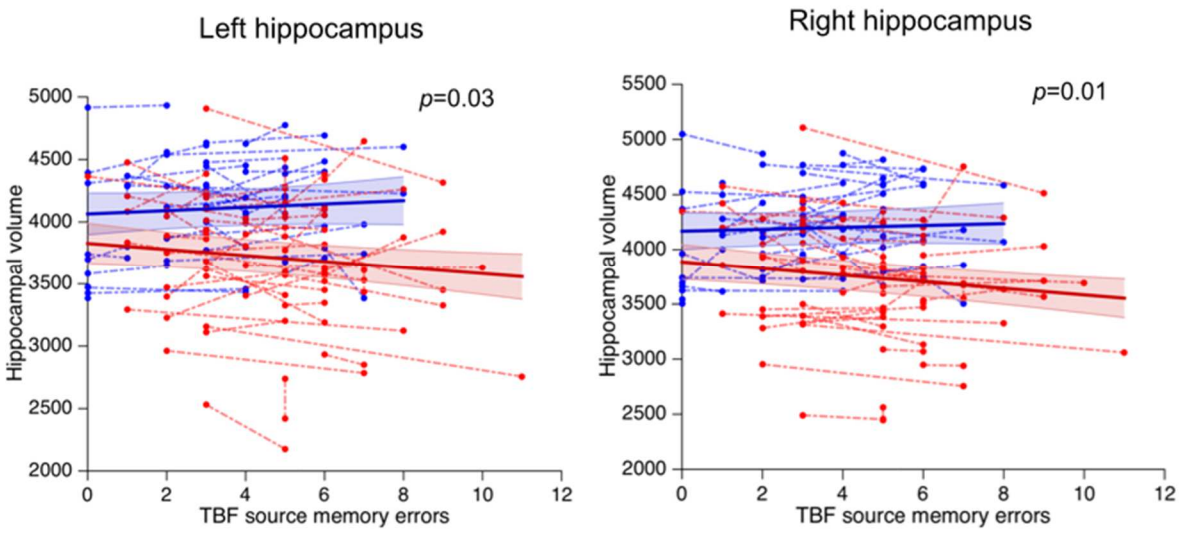


Figure 5. Correlation between changes in the number of cue memory errors and changes in hippocampal volume with age.

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= ((hits+0.5)/(hits + misses + 1)) x 100
False alarm rate = ((false alarms + 0.5)/(false alarms + correct rejection + 1)) x 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)
TBR 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.

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