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Long-term verbal memory deficit and associated hippocampal alterations in 22q11.2 deletion syndrome[a]

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Abstract

Background: 22q11.2 deletion syndrome (22q11DS) is a genetic disease associated with an increased risk for schizophrenia and a specific cognitive profile. In this paper, we challenge the current view of spared verbal memory in 22q11DS by investigating verbal memory consolidation processes over an extended time span to further qualify the neuropsychological profile. Our hypotheses are based on brain anomalies of the medial temporal lobes consistently reported in this syndrome.

Methods: 84 participants (45 with 22q11DS), aged 8-24 years old, completed a verbal episodic memory task to investigate long-term memory on four different time delays. We compared trajectories of forgetting between groups (22q11DS vs. controls) and analyzed performance inside the 22q11DS sample through cluster analyses. Potential links between memory performance and volume of the hippocampal subfields were examined.

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Results: We showed accelerated long-term forgetting (ALF) in the 22q11DS group, visible after a delay of one day. Using mixed models, we showed significant differences in the shape of memory trajectories between subgroups of participants with 22q11DS. These sub-groups differed in terms of memory recognition, intellectual functioning, positive psychotic symptoms and grey matter volume of hippocampal subfields but not in terms of age.

Conclusions: By investigating memory processes on longer delays than standardized memory tasks, we identified deficits in long-term memory consolidation leading to ALF in 22q11DS. Nevertheless, we showed that a subgroup of patients had larger memory consolidation deficit associated with lower intellectual functioning, higher rates of positive psychotic symptoms and hippocampal alterations.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic disorder associated with an increased risk for psychopathology and a specific cognitive profile (Henry et al., 2002; Schneider, Debbané, et al., 2014). Indeed, the presence of this microdeletion is recognized as one of the highest risk factors for the development of psychosis or schizophrenia spectrum disorder (Schneider, Debbané, et al., 2014).

Brain development abnormalities have been reported from a structural and functional perspective in this population (Gothelf, Schaer, & Eliez, 2008; Padula et al., 2017; Scariati, Padula, Schaer, & Eliez, 2016). More specifically, alterations of the medial temporal lobe, with a reduction of the body of the hippocampus have been consistently observed (Debbané, Schaer, Farhoumand, Glaser, & Eliez, 2006; DeBoer, Wu, Lee, & Simon, 2007; Eliez et al., 2001; Kates et al., 2006). Furthermore, in a mouse model of the human 22q11.2 microdeletion, alterations in the neuronal physiology of the hippocampus have been shown, suggesting decreased interneuron activity and deficits in long-term potentiation (Drew et al., 2011). As medial temporal lobes play a key role in memory functions, alterations have an impact on memory performance (Squire, Stark, & Clark, 2004).

On a behavioral level, a dissociation between verbal and visual memory processes has been described in 22q11DS. Indeed, probably due to poorer visuospatial and visuo-attentional processes, visual memory acquisition is not optimal and visual memory is generally reported as impaired (Bostelmann, Glaser, Zaharia, Eliez, & Schneider, 2017; Lajiness-O'Neill et al., 2005; Woodin et al., 2001). By contrast, it has been argued so far that verbal memory stands out as a relative strength in the 22q11DS cognitive profile (Jacobson et al., 2010; Lajiness-O'Neill et al., 2005; Lewandowski, Shashi, Berry, & Kwapil, 2007). However, while memory consolidation is known to occur over long delays such as weeks, months or even years (Squire & Alvarez, 1995), to our knowledge, no study has examined verbal memory performance on

delays beyond thirty minutes in the 22q11DS population. Therefore, although verbal learning performance seems relatively preserved, it is unknown whether long-term consolidation of memory is affected in 22q11DS. Interestingly, reports from individuals affected by 22q11DS and their families point to forgetfulness and memory loss over time, which challenges the general assumption of spared verbal long-term memory. We argue that longer recall delays need to be investigated in order to fully grasp verbal memory performance and consolidation processes in 22q11DS.

Memory consolidation can be defined as the neurobiological process of strengthening and stabilizing memories, which initially exist in an easily disrupted state (Bisaz, Travaglia, & Alberini, 2014). Once a memory has been consolidated, its reactivation through recall will revert the trace to a labile state. Another iteration of consolidation processes, known as reconsolidation, subsequently occurs in order to bring the memory trace back to a stable state (Alberini & Ledoux, 2013). When measuring forgetting, failure of consolidation or reconsolidation processes are assumed to lead to an accelerated long-term forgetting (ALF). ALF refers to the abnormally rapid pace at which memory fades, even though memories are encoded and retained normally over delays of thirty minutes (Elliott, Isaac, & Muhlert, 2014). Given that standardized tasks commonly used to assess episodic memory involve delays that do not exceed thirty minutes, an ALF phenomenon could go undetected using available tools.

On a behavioral level, memory consolidation can only be measured indirectly through retrieval. As retrieval can fail due to defects in accessing the memory (even if the memory is correctly stored), memory recognition paradigms are generally used as a complementary measure. It has been shown that memory recognition is based on two components: recollection and familiarity (Mandler, 1980; Squire et al., 2004). The latter is quickly accessible, contains no information about the context and depends on more adjacent cortex, whereas the former provides context

of encounter and depends mainly on the hippocampus (Eichenbaum, Yonelinas, & Ranganath, 2007; Squire et al., 2004).

Studying the characteristics of memory consolidation in 22q11DS is not only relevant for the understanding of the neuropsychological profile of the syndrome but may also provide important insights regarding preclinical stages of psychosis. Indeed, cognitive impairments, including episodic memory deficits, are reported as one of the core features of psychosis and schizophrenia spectrum disorders (Antoniades et al., 2017; Jahshan, Heaton, Golshan, & Cadenhead, 2010). Signs of memory deficits have also been reported in prodromal stages of schizophrenia as well as first-episode patients, and seem to be stable throughout the stages of the disease (Bora & Murray, 2014). Episodic memory deficits could therefore be considered as an endophenotype or an intermediate phenotype in the development of psychosis (Cannon, 2005; Owens et al., 2011). In line with this, studying episodic memory consolidation in a population at high risk for schizophrenia such as 22q11DS could help understand factors of interest in the emergence of psychosis.

Finally, despite a similar genetic etiological origin, relatively high levels of heterogeneity can be observed amongst individuals with 22q11DS in terms of their phenotypical expression (Philip & Bassett, 2011; Swillen & McDonald-McGinn, 2015). Therefore, when aiming at a fine-grained understanding of the syndrome, but also when seeking accurate predictors of later outcome, it becomes relevant to move beyond group comparisons (patients against controls). In line with this, several studies have attempted to identify subgroups of patients based on different variables (e.g., Sinderberry et al., 2013; Weinberger et al., 2016). However, the characterization of subgroups based on long-term memory consolidation has not yet been performed in 22q11DS.

1.1. Aims and hypothesis

In the present study, we first aimed to investigate long-term memory processes in 22q11DS and controls. Due to the deficit reported in visuo-attentional processes, possibly influencing the encoding of visual information, we focused on the verbal modality for which encoding seems to be relatively preserved (Debbané, Glaser, & Eliez, 2008). As previous studies showed preserved verbal memory performance using standardized tools after a delay of thirty minutes, we extended the recall delays to one day, one week and one month. Our first hypothesis was that verbal memory recall would be similar to controls after a delay of thirty minutes but lower on longer delays, which would represent indicators of an ALF phenomenon in this population. Additionally, since retrieval processes involved in free recall can sometimes be deficient, we also explored recognition memory as a complementary measure of memory consolidation. We predicted that if consolidation processes were altered, trajectories of recognition through time would follow the same path. Indeed, familiarity processes would not help recognition performance and a decline will also appear after a delay of time.

Our second aim was to determine whether subgroups of patients could be identified based on their long-term verbal memory profile. We hypothesized that alterations in the trajectory of memory retention would not be ubiquitous to 22q11DS but could selectively affect a sub-group of patients. Furthermore, in line with findings reporting an association between verbal memory impairments and psychosis (Owens et al., 2011), we hypothesized that individuals with poorer memory consolidation performance would display higher rates of psychotic symptoms.

Finally, the third aim was to investigate neural correlates of the behavioral findings. We hypothesized more important rates of volumetric reductions of the medial temporal lobe, in individuals with poorer performance on the memory task.

2. Method

2.1. Participants

Eighty-four participants (of which 45 with 22q11DS) completed an extensive series of assessments including cognitive functioning, clinical symptomatology and brain imaging as part of an ongoing longitudinal study on 22q11DS (Geneva cohort) (e.g., Schaer et al., 2009; Schneider, Van der Linden, et al., 2014). Participants were recruited through advertisement in patient association newsletters and word-of-mouth. The presence of a 22q11.2 deletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). The control group consisted of siblings from participants affected with 22q11DS (84%) and community controls. Participants with 22q11DS and controls were aged between 8 and 24 years and did not differ in terms of age or gender (see Table 1). Written informed consent, based on protocols approved by the Swiss Ethical Committee of Geneva (CCER, Switzerland), was obtained for all participants and their parents (if the participant was younger than 18 years old).

Table 1 Participant characteristics, psychiatric diagnosis and psychotropic medication

			Diagnostic group		Comparison		
			22q11DS	Controls	ANOVA	Pearson's Chi-square	p-value
N			45	39			
Gender (male (%))			20 (44.444%)	16 (41.025%)		0.1	0.082
Age (mean (SD))			16.050 (4.942)	14.166 (5.039)	2.981		0.088
Full Scale IQ (mean (SD))			71.444 (13.560)	114.487 (15.231)	187.736		**<0.001**
Psychiatric diagnosis (N (%))		Simple phobia	13(28.888%)				
		Attention deficit disorder	14 (31.111%)				
		Generalized anxiety	9 (20%)				
		Major depressive episode	2 (4.444%)				
		Psychosis	4 (8.888%)				
		Obsessive-compulsive disorder	1 (2.222%)				
Psychotropic medication (N(%))	Total		17 (37.777%)				
	Categories	Methylphenidate	11 (24.444%)				
		Antidepressants	8 (17.777%)				
		Antipsychotics	9 (20%)				
		Antiepileptic	0 (0%)				
		Anxiolytics	1 (2.222%)				

Significant values at the 0.05 level are displayed in **bold**

2.2. Material

2.2.1. Long-term memory task

To assess verbal episodic memory, we created a word-learning task, inspired by the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958). Task design and different steps is summarized in supplementary materials, Figure S1. We used the four wordlists of the RAVLT (A, B, C & D) as targets. Created to be of equal difficulty, these lists consisted in frequent

words from the French language (see Supplementary material, Table S1). Learning phase: words were read out loud by the examiner at a regular rhythm of 1 per 3 seconds. To limit the influence of working memory on outcome, a short filler task was performed at the end of each presentation, before proceeding with the recall. The filler task consisted in backwards counting (e.g., 100-1; 200-2; 300-6) during 30 seconds. To avoid recency or primacy effects, stimuli were read in a randomized order, different at each trial. The complete list of 15 words was read at each presentation. After the filler task, participants were instructed to freely recall as many words as they could remember, even those already recalled in a previous learning trial, in the order they chose. Productions were classified as correct (target word) or incorrect (non-target word or repetition of a word already said), no feedback was provided. To avoid over-learning or discouragement to the task, an 80%-success criterion (12 words) or a maximum of 6 trials was established, at which point the learning phase was over. Variables of interest for this phase were: number of presentation of the words to reach the criterion (trial to reach criterion) and maximum of correct words recalled at any stages of the learning phase (word max learned). Recall and recognition phase: participants were asked to freely recall the words after four different time delays (thirty minutes, one day, one week and one month). Again, productions were classified as correct (target word) or incorrect (non-target word or repetition of a word already said). After each free recall without feedback, participants were asked to recognize the 15 target words mixed with 15 distractors (see supplementary material, Table S2). The distractors consisted in words that were semantically or phonetically similar to the targets (see Supplementary material, Table S3) and were different for each delay (thirty minutes, one day, one week, one month) to avoid a familiarity effect from delay to delay. Variables of interest for this phase were: number of words freely recalled at each delay (free recalls at thirty minutes, one day, one week and one month) and number of words correctly recognized as target or distractor (recognition at thirty minutes, one day, one week and one month).

To really grasp the consolidation of memory over long periods of time, this study design extends over a month and beyond experimental conditions provided by laboratory testing. Indeed, only the first steps of the task (learning phase and thirty minutes recall) were conducted in laboratory setting. Recalls and recognitions after delays of one day, one week and one month were conducted remotely, via Skype© (Microsoft). We attempted to control for most external factors with the following measures: (1) the long-term memory task was done with the same examiner from the first to the last step; (2) stimuli were stored in a box and a reference to the box was made every time the words were recalled (e.g., "*Do you remember this box, what was in it. Can you remember the words I read to you that were stored in this box*"); (3) for recalls at delays of one day, one week and one month, an appointment was set with the participants on Skype but no specific information on what was going to happen was shared with the participant; (4) during Skype appointments, several misleading tasks (answering general knowledge questions, visual reasoning matrix completion) were done with the participant before or after the recall and recognition task so that the program of the next appointment could not be expected; (5) at the end of the last step (one month delay), we asked the participants (a) if they expected the purpose of the Skype appointments, and (b) if they had used a specific strategy to learn or remember the words they were presented with.

2.2.2. Measure of intelligence

All participants completed a Wechsler scale of intelligence to assess reasoning abilities. Children and adolescents up to 16 years old completed the Wechsler Intelligence Scale for Children (WISC-III or IV; Wechsler, 1991, 2004). Participants from 17 years and up completed the Wechsler Adult Intelligence Scale (WAIS-III or IV; Wechsler, 1997, 2011).

2.2.3. Clinical assessment: All participants with 22q11DS and their caregivers were interviewed by a trained psychiatrist using the computerized Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000) or the Structured Clinical Interview for

DSM-IV Axis I (SCID-I; First, Spitzer, & Williams, 1996). The psychotic disorders supplement of the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was also administered to all participants. Psychotic symptoms were assessed using the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2004), as well as the Positive And Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opier, 1967) and the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Positive and negative dimension were compared individually, for the SIPS, we also examined the disorganized dimension; and for the PANSS we compared the negative symptoms through the amotivation dimension and the expressive dimension based on previous work from our lab (Schneider, Van der Linden, et al., 2014). Information about the presence of psychiatric diagnoses and use of psychotropic medication at the time of testing is summarized in Table 1.

2.2.4. Neuroimaging

Neuroimaging was available in 35/45 patients who underwent verbal memory assessment. T1-weighted structural MRI images were acquired using a three-dimensional volumetric pulse sequence with Siemens Trio 3T scanners (sequence parameters: TR=2500ms, TE=3ms, flip-angle=8°, acquisition matrix=256×256, field of view=22cm, slice thickness=1.1mm, and 192 slices). Images were imported in FreeSurfer software package version 6.0 (https://surfer.nmr.mgh.harvard.edu/) for an automated segmentation of hippocampal subfields and total hippocampal volume (Iglesias et al., 2015). The approach makes use of an atlas constructed from high very high resolution ex-vivo images with Bayesian inference to segment the hippocampus in 12 subfields: Parasubiculum, Presubiculum, Subiculum, CA1, CA2/3, CA4, Granulate Cells of the Molecular Layer of the Dentate Gyrus (GC-ML-DG), Molecular Layer, Hippocampal Fissure, Fimbria, Hippocampal Tail, and Hippocampus-Amygdala Transition Area (HATA) (Iglesias et al., 2015). The quality of the segmentation was checked

as explained in (Mancini et al., 2019). Measures of supra-tentorial brain volume were also extracted using FreeSurfer.

2.3. Statistical analyses

2.3.1. Memory performance and memory retention trajectory

Learning performance variables (assessed by "trial to reach criterion" and "word max learned") were not normally distributed (respectively, for 22q11DS: D(45) = 0.244, p <0.001; D(45) = 0.235, p <0.001; for Controls: D(39) = 0.203, p <0.001; D(39) = 0.304, p <0.001;) therefore compared between groups using non-parametric tests (Mann-Whitney test). Trajectories of memory retention and recognition over time were examined using mixed models regression analyses in MATLAB R2014 (MathWorks), as described in previous studies (Franchini et al., 2018; Mancini et al., 2019; Mutlu et al., 2013). These analyses allowed us to identify shape differences (i.e., curves that do not follow the same path) or intercept differences (i.e., curves that follow a parallel path but not on the same intercept) between two groups (22q11DS vs. controls or subgroups within 22q11DS). In complementary analyses, IQ, age, and IQ + age were used as covariates. Groups were then compared on a series of variables (age, intellectual functioning, positive and negative psychotic symptomatology) using non-parametric tests (Mann-Whitney test and Wilcoxon signed rank test). The influence of age on general memory performance was examined using Spearman correlations. The Benjamini-Hochberg (Thissen, Steinberg, & Kuang, 2002) multiple comparison correction was applied to all statistical analyses. For non-parametric tests, effect sizes were calculated using eta square formula. For the mixed models, the p-values are derived with a likelihood ratio test comparing the full models (including group-by-intercept effect respectively a group-by-shape effect) to the reduced models (without the respective group effects). Details on the fitted models as well as likelihood ratios are summarized in Table 2.

Table 2: Differences in trajectories of memory retention and recognition between groups of 22q11DS and Control

			Group effect		Slope	
	22q11DS intercept, beta1, beta2 (SD)	Controls intercept, beta1, beta2 (SD)	Likelihood ratio (df)	Group effect (*p*-value)	Likelihood ratio (df)	*p*-value
Memory retention (raw score)	12.394(+/-0.260), -2.163(+/-0.247), 0.186(+/-0.056)	12.586(+/-0.279), -1.477(+/-0.266), 0.152(+/-0.060)	14.933(3)	0.002	11.350(2)	0.003
Memory retention (raw score) covariate with IQ	13.491(+/-0.308), -2.163(+/-0.248), 0.186(+/-0.056)	11.320(+/-0.341), -1.477(+/-0.266), 0.152(+/-0.060)	22.184(3)	<0.001	12.197(2)	0.002
Memory retention (raw score) covariate with age	12.3351(+/-0.259), -2.163(+/-0.247), 0.186(+/-0.056)	12.636(+/-0.278), -1.477(+/-0.266), 0.152(+/-0.060)	15.940(3)	0.001	11.293(2)	0.004
Memory retention (raw score) covariate with age and IQ	13.441(+/-0.306), -2.163(+/-0.247), 0.186(+/-0.056)	11.378(+/-0.339), -1.477(+/-0.266), 0.152(+/-0.060)	21.093(3)	<0.001	12.136(2)	0.002
Recognition (raw score)	29.161(+/-0.399), 0.552(+/-0.368), -0.239(+/-0.072)	30.006(+/-0.429), -0.140(+/-0.396), -0.032(+/-0.077)	13.334(3)	0.004	11.168(2)	0.004
Recognition (raw score) covariate with IQ	30.591(+/-0.223), -0.642(+/-0.084)	29.895(+/-0.246), -0.300(+/-0.091)	7.723(3)	0.021	7.492(2)	0.006
Recognition (raw score) covariate with age	29.151(+/-0.340), 0.552(+/-0.368)	30.019(+/-0.428), -0.140(+/-0.394)	13.580(3)	0.004	11.168(2)	0.004
Recognition (raw score) covariate with age and IQ	29.3728(+/-0.423), 0.552(+/-0.370)	29.7622(+/-0.457), -0.140(+/-0.398)	11.504(3)	0.009	11.359(2)	0.003

beta1 = linear time effect of trajectory
beta2 = quadratic time effect of trajectory
SD = Standard Deviation

2.3.2. Clustering of Patients According to Trajectories of Memory Retention:

The k-means clustering method was used to split the patients' sample into two subgroups based on their memory retention performances. Recall scores at each time delay were defined as the grouping variables. The algorithm groups together subjects with a similar variable of interest throughout multiple observations by minimizing the distance between each observation point and the mean of the class (Twisk & Hoekstra, 2012). In this context the algorithm yielded groups of individuals with similar memory retention performance across multiple assessments, indicating similar longitudinal trajectories of memory retention over time. We specifically employed K-means clustering as implemented in Matlab, with 10000 iterations, yielding subgroups of subjects with similar trajectories of memory retention. We subsequently employed linear mixed model regression (Mutlu et al., 2013) to compare subgroups of patients to each other and to healthy controls according to trajectories of memory retention and recognition. In the mixed models analyses, we added a complementary analysis with age as a covariate for memory retention and recognition. Subgroups of patients were furthermore compared to each

other according to clinical and neuropsychological variables of interest as well according to measures of hippocampal morphology. Again, the Benjamini-Hochberg multiple comparison correction was applied to all statistical analyses. Effect sizes are displayed on Table 5 and details on the fitted models as well as likelihood ratios are summarized in Table 4.

2.3.3. Neuroimaging

Grey matter volume of hippocampal subfields as well as of the whole hippocampus were compared between clusters of patients divided according to their trajectory of memory retention. Statistical differences were evaluated non-parametrically using Wilcoxon rank sum test after accounting for the effect of age, gender, supra-tentorial brain volume and performance IQ with linear regression. Effect sizes were computed using Hedges' g.

3. Results

3.1. Group comparison (22q11DS vs. typically developing controls)

3.1.1. Learning

Mann-Whitney tests indicated that there was no significant difference in the amount of trials needed to reach the learning criterion between groups ($Mdn_{22q11DS} = 3$, $Mdn_{Ctrl} = 3$, $U = 718.500$, $z = -1.470$, $p = 0.142$, $\eta^2 = 0.026$), nor in the maximum amount of words recalled at the end of the learning phase ($Mdn_{22q11DS} = 12$, $Mdn_{Ctrl} = 12$, $U = 729.500$, $z = -1.416$, $p = 0.157$, $\eta^2 = 0.024$). Therefore, learning performance is comparable between the two groups.

3.1.2. Recall

we compared trajectories of free recall performance throughout each time delay (thirty minutes, one day, one week and one month) in 22q11DS and controls using mixed models regression (Figure 1A). We observed a significant difference in the shape of the trajectories with time ($p = 0.002$; see Table 2 for details). When full-scale IQ was entered as a covariate in the analyses, the difference in shape remained significant ($p < 0.001$), characterized by a steeper forgetting

slope in the 22q11DS group with time. The same observation was made for age in covariate ($p = 0.001$) and combined age and full-scale IQ ($p < 0.001$). With Mann-Whitney tests we showed that both groups had similar recall performance after thirty minutes ($Mdn_{22q11DS} = 11$, $Mdn_{Ctrl} = 11$, $U = 874.500$, $z = -0.027$, $p = 0.978$, $\eta^2 < 0.001$), After Benjamini-Hochberg correction (new threshold for statistical significance $p < 0.013$), the control group had significantly higher scores than the 22q11DS group after one day ($Mdn_{22q11DS} = 9$, $Mdn_{Ctrl} = 10$, $U = 511.000$, $z = -3.316$, $p = 0.001$, $\eta^2 = 0.132$) and one month ($Mdn_{22q11DS} = 7$, $Mdn_{Ctrl} = 10$, $U = 506.500$, $z = -3.345$, $p = 0.001$, $\eta^2 = 0.135$). The difference between group at one week was significant ($Mdn_{22q11DS} = 8$, $Mdn_{Ctrl} = 9$, $U = 609.000$, $z = -2.427$, $p = 0.015$, $\eta^2 = 0.071$), but did not survive multiple comparison. Analyzing the dynamic of memory loss through post-hoc comparisons confirmed the presence of different trajectories between groups. In the control group, using Wilcoxon signed rank tests, after Benjamini-Hochberg correction (new threshold for statistical significance $p < 0.025$), a significant drop in performance was observed between one day and one week ($Mdn_{one\_day} = 10$, $Mdn_{one\_week} = 9$, $Z = -3.788$, $p < 0.001$, $\eta^2 = 0.378$), whereas comparisons between thirty minutes and one day or one week and one month did not differ ($p > 0.778$). As for the 22q11DS group, performance dropped significantly between each time delay ($Mdn_{thirty\_min} = 11$, $Mdn_{one\_day} = 9$, $Z = -4.308$, $p < 0.001$, $\eta^2 = 0.422$; $Mdn_{one\_day} = 9$, $Mdn_{one\_week} = 8$, $Z = -4.066$, $p < 0.001$, $\eta^2 = 0.376$) and tended to stabilize between one week and one month ($Mdn_{one\_week} = 8$, $Mdn_{one\_month} = 7$, $Z = -1.966$, $p = 0.049$, $\eta^2 = 0.088$) since the comparison did not survive multiple comparison correction (new threshold for statistical significance $p < 0.008$).

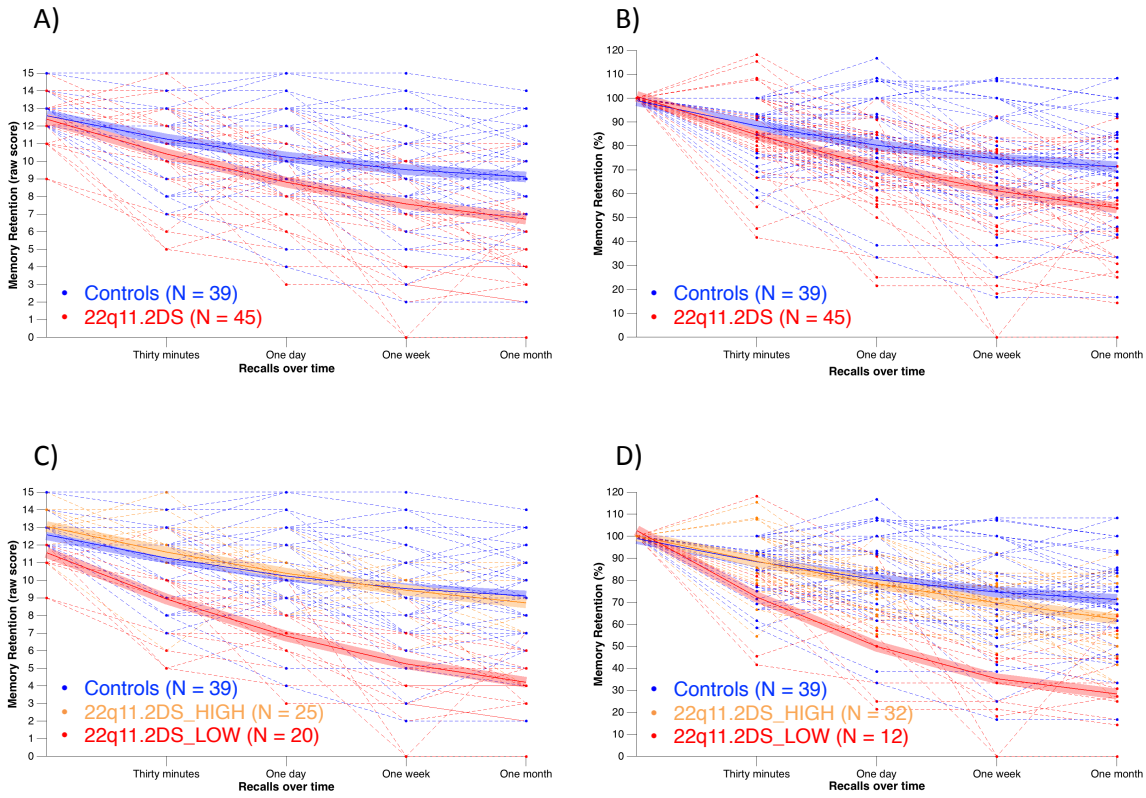

Figure 1: Group comparison of long-term memory trajectories through time

3.1.3. Recognition

we compared both groups on correct recognition performance, using the amount of words correctly identified as target or distractor (total of 30). There was a significant difference in shape of the trajectories with time ($p = 0.004$) (Figure 2A; see Table 2 for details). Results were similar after adding full-scale IQ ($p = 0.021$), age ($p = 0.004$) as well as full-scale IQ combined ($p = 0.009$) as covariates. A Mann-Witney test indicated that, after multiple comparison correction (new threshold for statistical significance $p < 0.018$) there was poorer recognition performance in the 22q11DS group at thirty minutes ($Mdn_{22q11DS} = 30$, $Mdn_{Ctrl} = 30$, $U = 664.500$, $z = -2.483$, $p = 0.013$, $\eta^2 = 0.074$) and one month delay ($Mdn_{22q11DS} = 28$, $Mdn_{Ctrl} = 30$, $U = 508$, $p = 0.001$, $\eta^2 = 0.141$).

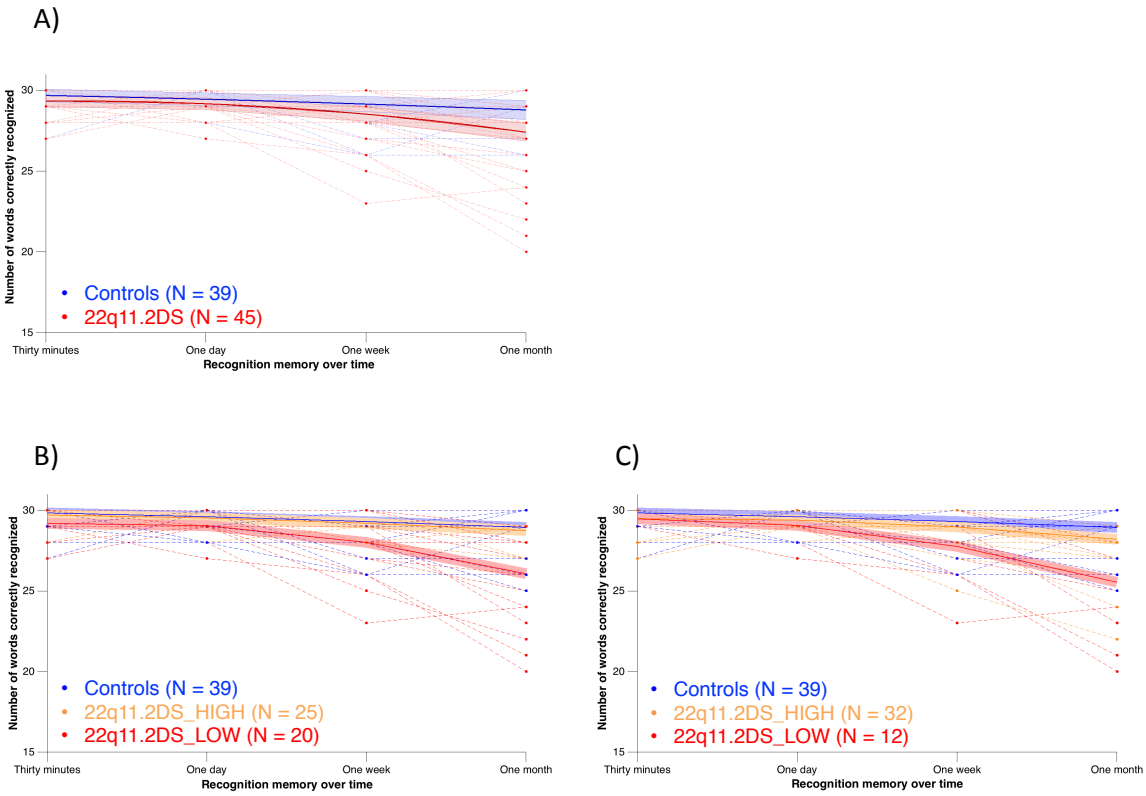

Figure 2: Group comparison of recognition memory trajectories through time

3.1.4. Strategy analysis

during the learning phase, only 7 individuals (7.9%) reported the use of a specific strategy to learn the words. From this sample 5 (1 individual with 22q11DS) tried to do semantic associations and 2 (none with 22q11DS) used mental imaging to remember the words. For memorization, on the whole sample, approximatively half of the participants (48.9%) reported they knew they would have to repeat the words later on. There was no difference between 22q11DS and control participants on this matter (χ^2 [1, 88] = 0.164, p = 0.686). Even with half of the sample anticipating the purpose of the task, only 12 participants (13.6%) told us they tried to remember the words in between recalls, mostly just a few minutes before the skype meeting. Both groups did not differ on this with 6 participants in each diagnostic group (χ^2 [1, 88] = 0.182, p = 0.670). No participant reported writing down the words to remember them.

3.2. Correlation with age

As memory performance is reported to increase with age, we investigated the link between age, learning and memory performance in individuals with 22q11DS and typically developing controls using a Spearman one-tailed correlation. Interestingly, almost all the variables reflecting learning and free recall performance in the control group were significantly associated with age (see Table 3). In the 22q11DS group however, only the number of trials needed to reach criterion was significantly associated with age ($r = -2.92$; $p = 0.026$). Recognition performance at any delay was not related to age in either of the two groups.

Table 3 Correlation of memory performance with age

	22q11DS		Controls	
	Age		Age	
	Spearman Correlation	*Sig (1-tailed)*	*Spearman Correlation*	*Sig (1-tailed)*
Number of learning trials	-.292**	0.026	-.453**	0.002
Maximum number of words recalled in learning phase	-0.168	0.134	.320**	0.024
Free recall thirty minutes delay	-0.103	0.251	.449**	0.002
Recognition thirty minutes delay	0.054	0.361	0.116	0.242
Free recall one day delay	-0.005	0.488	.433**	0.003
Recognition one day delay	0.01	0.473	-0.027	0.435
Free recall one week delay	-0.13	0.197	0.219	0.09
Recognition one week delay	-0.14	0.179	-0.112	0.249
Free recall one month delay	-0.097	0.263	.291*	0.036
Recognition one month delay	-0.088	0.283	-0.071	0.335

*** Correlation is significant after Benjamini-Hochberg correction at the 0.027 level (1-tailed)*
** Correlation is significant at the 0.05 level (1-tailed)*

3.3. Cluster analyses

3.3.1. Clustering with raw scores of memory

To account for the heterogeneity of performance in the 22q11DS sample, we performed a cluster analysis to discriminate more homogeneous subgroups of individuals based on raw recall performance. The sample was split in two subgroups, one of 25 individuals having higher global memory performance (22q11DS_HIGH) and another of 20 individuals having lower memory performance (22q11DS_LOW). When comparing their trajectories of memory recalls though time, we found a significant difference in shape ($p < 0.001$) between the two clusters (Figure 1C; see Table 4 for details). Furthermore, both groups differed on learning performance, with a significantly higher number of words recalled at the end of the learning phase ($p < 0.001$,

η^2 = 0.328) for the 22q11DS_HIGH group, but a comparable number of trials to reach the learning criterion (p = 0.119, η^2 = 0.055; see Table 5). Finally, the 22q11DS_HIGH group exhibited no difference in shape or intercept of memory performance with the control group, whereas the 22q11DS_LOW group had a significant difference in shape of memory performance with the control group (p < 0.001). Post-hoc non-parametric group-comparisons showed that participants from the two clusters were comparable in age (p = 0.798, η^2 = 0.001), but differed on intellectual functioning (F [1,44] = 14.844, p < 0.001, η^2 = 0.257) and one measure of positive psychotic symptoms (the other ones did not survive the Benjamini-Hochberg correction with a significant threshold at 0.026, see Table 5). No difference was seen with negative psychotic symptoms. The group with lower long-term memory performance had significantly lower IQ and increased positive symptoms. In regards to recognition memory, we compared both clusters on trajectories over time using mixed models. We found a significant difference in shape (p < 0.001; see Table 4 for details) between the two clusters (Figure 2B).

Table 4: Differences in trajectories of memory retention and recognition between clustered groups of 22q11DS HIGH and LOW

	Raw clustering		Group effect		Slope	
	22q11DS_HIGH intercept, beta1, beta2 (SD)	22q11DS_LOW intercept, beta1, beta2 (SD)	Likelihood ratio (df)	Group effect (*p*-value)	Likelihood ratio (df)	*p*-value
Memory retention (raw score)	13.054(+/-0.302), -1.575 (+/-0.334), 0.123(+/-0.079)	14.539(+/-0.692), -0.254(+/-0.764), 0.019(+/-0.181)	63.311(3)	<0.001	20.883(2)	<0.001
Memory retention (raw score) covariate with age	12.3351(+/-0.259), -2.163 (+/-0.247), 0.186(+/-0.056)	12.636(+/-0.278), -1.477(+/-0.266), 0.152(+/-0.060)	64.305(3)	<0.001	21.214(2)	<0.001
Recognition (raw score)	29.750(+/-0.645), 0.026(+/-0.593)	31.075(+/-1.479), -1.158(+/-1.358)	21.947(3)	<0.001	18.417(2)	<0.001
Recognition (raw score) covariate with age	29.751(+/-0.645), 0.026(+/-0.592)	31.078(+/-1.477), -1.158(+/-1.357)	21.893(3)	<0.001	18.409(2)	<0.001
	Normalized Clustering		Group effect		Slope	
	22q11DS_HIGH intercept, beta1, beta2 (SD)	22q11DS_LOW intercept, beta1, beta2 (SD)	Likelihood ratio (df)	Group effect (*p*-value)	Likelihood ratio (df)	*p*-value
Memory retention (raw score)	100.174(+/-1.861), -12.281(+/-2.250), 0.705(+/-0.528)	97.747(+/-4.955), 9.506(+/-5.992), -2.467(+/-0.528)	55.617(3)	<0.001	37.607(2)	<0.001
Memory retention (raw score) covariate with age	100.129(+/-1.863), -12.281(+/-2.250), 0.705(+/-0.528)	97.518(+/-4.972), 9.506(+/-5.991), -2.467(+/-1.407)	55.209(3)	<0.001	37.722(2)	<0.001
Recognition (raw score)	30.074(+/-0.251), -0.426(+/-0.112)	28.920(+/+0.669), 0.456(+/-0.298)	14.915(2)	<0.001	14.478(1)	<0.001
Recognition (raw score) covariate with age	30.077(+/-0.251), -0.426(+/-0.112)	28.939(+/-0.671), 0.456(+/-0.298)	14.931(2)	<0.001	14.462(1)	<0.001

beta1 = linear time effect of trajectory
beta2 = quadratic time effect of trajectory
SD = Standard Deviation

Specifically, there was a significant difference in shape between the cluster with low global memory performance (22q11DS_LOW) and the control group ($p < 0.001$), whereas the cluster with high global memory performance (22q11DS_HIGH) did not differ from the control group in shape or intercept.

3.3.2. Clustering with normalized scores of memory (retention percentage)

To exclude influence of learning, we performed a second cluster analysis in the 22q11DS sample using normalized scores that reflect a purer measure of memory retention. To obtain these normalized scores, we divided the raw performance at each time delay by the maximum number of words recalled at the end of the learning phase. We calculated a long-term memory retention percentage score that we used in the clustering. Using this variable, 33 individuals were included in the groups with higher performance (22q11.2D_HIGH) and only 12 had lower performance (22q11DS_LOW). Overall, there was a 76% of overlap with the previous analysis. With this new clustering, we observed a significant difference in the shape of the group's trajectories with time ($p < 0.001$; see Table 4 for details and Figure 1D). Post-hoc non-parametrical analyses showed that while both groups did not differ in terms of age ($p = 0.357$, $\eta^2 = 0.020$) or learning competence ($p > 0.094$, $\eta^2 < 0.069$), the 22q11DS_LOW group had lower intellectual functioning ($F [1,44] = 5.58$, $p = 0.023$, $\eta^2 = 0.114$) but no other difference in psychotic symptoms (see Table 5). Finally, when compared on recognition memory, results were similar to the previous clustering technique: there was a significant difference in shape ($p < 0.001$; see Table 4 for details) between the two clusters (Figure 2C) showing a larger decline in the 22q11DS_LOW cluster. The 22q11DS_HIGH cluster was not different in shape or intercept from the control group, whereas the 22q11DS_LOW cluster had a significantly different shape of trajectory ($p < 0.001$).

Table 5 Clustering in the 22q11DS group

	Raw clustering		Comparison				
	22q11DS_HIGH	22q11DS_LOW	Pearson's Chi-square	ANOVA	Mann-Witney	P-value	Effect size η^2
N	25	20					
Gender (male(%))	10(40%)	10 (50%)	0.45			0.502	
Age (mean (SD))	15.878 (4.768)	16.265 (5.269)		0.067		0.798	0.001
Full Scale IQ (mean(SD))	77.52 (12.689)	63.85(10.638)		14.844		**<0.001**	**0.257**
Number of learning trials (mean(SD))	3.480(1.294)	4.250(1.618)			184	0.119	0.055
Maximum number of words recalled in learning phase (mean(SD))	12.920(0.953)	11.400(1.313)			86.5	**<0.001**	**0.328**
BPRS positive symptoms (mean (SD))	1.733(0.659)	2.633(1.34599)			135	**0.007**	**0.163**
BPRS negative symptoms (mean (SD))	2.306(0.552)	2.350(1.017)			213.5	0.390	0.017
PANSS positive symptoms (mean (SD))	1.405(0.464)	1.914(0.932)			158	0.034	0.102
PANSS negative expressive (mean (SD))	2.456(0.736)	2.630(0.956)			230.5	0.655	0.005
PANSS negative amotivation (mean (SD))	2.820(0.945)	3.075(1.206)			221.5	0.506	0.010
SIPS disorganisation (mean (SD))	0.479(0.403)	1.166(1.224)			140.5	0.047	0.090
SIPS positive (mean (SD))	0.675(0.645)	1.333(1.321)			151	0.096	0.063
SIPS negative (mean (SD))	2.125(0.818)	2.379(0.957)			185.5	0.437	0.014
	Normalized clustering		Comparison				
	22q11DS_HIGH	22q11DS_LOW	Pearson's Chi-square	ANOVA	Mann-Witney	P-value	Effect size η^2
N	34	11					
Gender (male(%))	13 (28.235%)	7 (63.636%)	2.127			0.131	
Age (mean (SD))	15.660(4.579)	17.257(6.013)		0.866		0.357	0.020
Full Scale IQ (mean(SD))	74.029(12.929)	63.455(12.824)		5.58		**0.023**	**0.114**
Number of learning trials (mean(SD))	3.559(1.307)	4.636(1.747)			123	0.094	0.069
Maximum number of words recalled in learning phase (mean(SD))	12.353(1.353)	11.909(1.446)			145.5	0.277	0.038
BPRS positive symptoms (mean (SD))	1.990(0.881)	2.575(1.592)			148	0.293	0.025
BPRS negative symptoms (mean (SD))	2.245(0.593)	2.575(1.202)			171	0.663	0.004
PANSS positive symptoms (mean (SD))	1.550(0.556)	1.883(1.158)			184.5	0.947	<0.001
PANSS negative expressive (mean (SD))	2.476(0.741)	2.709(1.100)			171	0.671	0.004
PANSS negative amotivation (mean (SD))	2.882(0.985)	3.091(1.319)			179	0.829	0.001
SIPS disorganisation (mean (SD))	0.546(0.513)	1.500(1.452)			90.5	0.033	0.103
SIPS positive (mean (SD))	2.135(0.795)	2.550(1.091)			142.5	0.603	0.006
SIPS negative (mean (SD))	0.812(0.698)	1.420(1.692)			128.5	0.351	0.020

Significant values after Benjamini-Hochberg correction at the 0.026 level are displayed in **bold**

3.4. Neuroimaging

When comparing the volume of hippocampal subfields in subjects divided according to the trajectory of raw verbal memory retention (N-High=21 vs N-Low=14), we did not observe any significant difference neither in left or right global hippocampal volume nor in the volumes of any hippocampal subfield ($p > 0.07$). However, when comparing subjects divided according to the trajectory of normalized verbal memory retention (N-High=27 vs N-Low=8), patients with

steeper memory decline presented significant reductions of both the left (p = 0.039, g = 0.76) and right (p = 0.021, g = 0.95) global hippocampal volume (see Supplementary materials, Figure S2). Such global decline was driven by significant reductions at the level of the bilateral CA3 (p_left = 0.047, g_left = 0.80, p_right = 0.01, g_right = 0.92), CA4 (p_left = 0.023, g_left = 0.95, p_right = 0.008, g_right = 1.1), dentate gyrus (p_left = 0.032, g_left = 0.92, p_right = 0.009, g_right = 1.1) and molecular layer (p_left = 0.015, g_left = 0.84, p_right = 0.012, g_right = 1.1), as well as left CA1 (p = 0.021, g = 0.67) and right subiculum (p = 0.029, g = 0.81).

4. Discussion

The overall aim of the present study was to investigate verbal episodic memory processes and to further characterize the consolidation of memory in a population at high risk of cognitive deficits and psychopathology. By exploring memory performance on longer delays than standardized memory testing batteries (one day, one week, one month), we set out to shed further light on abnormal memory consolidation patterns in 22q11DS compared to a control population. Overall, although reported as a relative strength in 22q11DS, when tested on delays exceeding thirty minutes, verbal memory processes were impaired, providing first evidence for an ALF in this population.

4.1. Evidence for an accelerated long-term forgetting when compared with controls

4.1.1. Comparable learning performance

We showed that in a verbal episodic memory task, participants with 22q11DS acquired the same amount of words and at the same pace than the control group. This is in line with previous work showing preserved verbal encoding in 22q11DS (Debbané et al., 2008). Furthermore, studies using global memory batteries showed that participants with 22q11DS obtained immediate verbal memory scores that were in the normal range (Campbell et al., 2010;

Lajiness-O'Neill et al., 2005). Together these results suggest preserved verbal learning performance in this population.

4.1.2. Shape difference in memory trajectories through time

When trajectories were examined through time, we found a significant shape difference between groups. Indeed, our results showed similar memory performance between groups at the standard delay of thirty minutes after the learning phase, but on longer delays, a significant drop in performance was observed in the 22q11DS group, suggesting abnormal consolidation processes. Thus, our first hypothesis of an ALF phenomenon in this population was supported. This finding has important conceptual and clinical implications, as it challenges the current literature on verbal long-term memory. Indeed, until now, consolidation processes were typically considered to be preserved in 22q11DS, since immediate recall and thirty minutes delayed recall were found to be in the normal range (Lajiness-O'Neill et al., 2005). Using adapted tools for the assessment of long-term consolidation processes, we were however able to demonstrate a considerable ALF phenomenon that has been overlooked thus far and may involve underestimated educational or daily life challenges for affected individuals. These results highlight how current clinical assessment tools should be adapted to fully grasp memory processes in this population (Elliott et al., 2014). It also brings considerations around clinical patient management and future intervention targets tailored to this population. Indeed, educational and professional arrangements, such as limiting the amount of information to be memorized by heart and provide with memory aids, or regular reminders of previously learned information, could be useful.

4.1.3. Recognition processes

To our knowledge, this is the first paper to compare recall and recognition performance in one single design. When recognition memory performance was examined though time, we observed a similar pattern of decline as for recall performance. Post-hoc analyses however indicated that

the decline in recognition performance was significant after a delay of thirty minutes and one month. From these results, one might infer that familiarity processes are weaker in 22q11DS. This conclusion would be in line with previous research showing deficits in source monitoring (Debbané et al., 2008). Thus, we have shown for the first time similar patterns of decline in recall and recognition performance in this population.

4.1.4. Lack of improvement with age in the 22q11DS group

When we examined the influence of age on long-term memory processes, we did not find any correlation with age in the 22q11DS group. This result contrasts with a positive correlation between age and performance in the control group, with older individuals performing better at the memory task. One possible explanation for this result is that verbal long-term memory skills do not evolve as drastically with age as in typically developing individuals. Therefore, young participants may perform similarly to older participants. These results could suggest that performance reach a developmental plateau much faster than the control group. To our knowledge, although similar results have been previously shown for other cognitive domains (e.g. executive functions) in this population (Maeder et al., 2016), this question has never been investigated in the field of verbal long-term memory. Future studies should examine developmental trajectories of verbal long-term memory in 22q11DS.

4.2. Subgroups of memory patterns in the 22q11DS population

As for the second aim, our results showed that trajectories of verbal long-term memory were heterogeneous, in line with the literature describing a vast phenotype in 22q11DS (Philip & Bassett, 2011; Swillen & McDonald-McGinn, 2015). We used a cluster analysis with two different approaches to identify subgroups in this population.

In the first approach, raw long-term memory scores were used, since learning competences in the 22q11DS group were similar to those of controls. We extracted two subgroups with high and low long-term memory competence, respectively. Interestingly, the group with higher long-

term memory performance had a long-term memory trajectory resembling the curve of the control group. Conversely, the group with lower long-term memory had a significantly steeper decline in performance with time. These results suggest that there is a subgroup of participants driving the ALF effect that was observed in the comparison against controls. This subgroup with lower long-term memory also exhibited lower IQ and higher rates of positive psychotic symptoms. As measures of IQ rely partially on memorized information (Wechsler, 2011), this association was expected. Regarding the association of poor verbal long-term memory and psychotic symptoms, cognitive decline has been identified as a risk of developing a psychotic illness in 22q11DS (Vorstman et al., 2015). Nevertheless, previous studies have shown similar levels of intellectual functioning in a population affected by 22q11DS with predominant negative symptoms compared to a population having low levels of symptoms (Schneider, Van der Linden, et al., 2014). Thus, consistent with our results, positive symptoms rather than negative seem to be more related to cognitive deficits, especially for memory processes. Moreover, a study on hippocampal development in a partially overlapping sample of patients with 22q11DS demonstrated that only positive symptoms are correlated with hippocampal volume decrease during adolescence (Mancini et al., 2019).

To deepen our understanding of memory processes in these subgroups, we examined trajectories of memory recognition over time. We found a pattern comparable to recall performance, with lower recognition competences in the group with lower global memory performance. Again, previous work has already shown in a different task that familiarity (depending on source monitoring) is a weak point in this syndrome (Debbané et al., 2008). This brings additional evidence for a disappearance of the memory trace with time and suggests that low scores on long-term memory are not caused by difficulties in the retrieval process of memory traces.

As the first clustering approach yielded a slight (although insignificant) difference in learning performance between both 22q11DS groups (HIGH vs. LOW), we conducted a second cluster analysis after normalizing long-term memory performance for learning. This procedure allowed us to directly isolate the consolidation processes at stake in this task and prevented potential biases due to differential learning performances. Clustering also yielded two subgroups with significantly different long-term memory performance. More specifically, using the normalized memory performance as a clustering input, we found a smaller subgroup of patients with lower long-term memory performance who exhibited an unexpected long-term memory trajectory. Interestingly, this subgroup had a significant drop already visible after a delay of thirty minutes, which does not typically qualify as an ALF phenomenon. These results suggest that although these individuals were able to learn the words that were presented, consolidation (short-term and long-term) processes did not occur properly, leading to the gradual disappearance of the trace in memory. Furthermore, this subgroup with less efficient consolidation had a significantly lower IQ than the other 22q11DS subgroups and a trend to higher positive disorganization symptoms. As mentioned before, numerous aspects of intelligence are evaluated through previously memorized knowledge (especially in the verbal scales), and the association between poor memory performance and IQ is therefore not surprising. Moreover, as the participants in this group also exhibited memory loss on shorter delays (thirty minutes), lower scores on general intelligence could be expected. As for the larger group with higher long-term memory performance, it was characterized by a pattern of forgetting that resembled controls. Finally, we compared recognition memory trajectories in both clusters to further understand performance in these groups. Results were very similar to the ones obtained in the first clustering procedure. Indeed, the subgroup with lower performance on recall through time also had poorer recognition performance with scores dropping rapidly through time. Again,

these results converge to poorer memory performances that are neither supported by familiarity nor recollection.

4.3. Neuronal correlates of verbal memory performance in 22q11DS

As for our third aim, when clustering patients according to raw memory scores, we did not find any difference in hippocampal anatomy between groups. However, when normalizing retention scores for learning, the subgroup of patients presenting both short-term and long-term accelerated memory decline presented significant smaller bilateral hippocampal volume driven by largely symmetric volumetric reductions affecting several hippocampal subfields, including CA3, CA4 and dentate gyrus. Hippocampal differences were observed only when normalizing for learning and remained significant after controlling for overall cognitive performance. This suggests that hippocampal alterations may specifically affect memory consolidation. This finding is in line with previous work on the hippocampus showing that this cortical structure is essential for the early phases of memory consolidation (Frankland & Bontempi, 2005). Difficulties in the learning phase are, on the other hand, more likely related to other neurodevelopmental alterations previously described in 22q11D.2S, such as accelerated cortical thinning, or altered structural and functional cortical connectivity (Padula et al., 2017; Scariati et al., 2016; Schaer et al., 2009). More specifically, the earliest working-memory phase of memory acquisition largely depends upon fronto-parietal cortical networks, and connectivity alterations of this network have been specifically related to working memory deficits in 22q11DS (Sandini et al., 2018). Thus, while fronto-parietal anomalies are likely related to impairments in the learning phase of memory processes, hippocampal anomalies appear to be specifically associated to altered memory consolidation, visible in our sample through an accelerated memory decline starting from thirty minutes post-acquisition.

4.4. Limits and future directions

This study comes with some limitations. First of all, the age-related data presented here is from a cross-sectional approach, with a relatively large age range. However, in order to identify specific developmental patterns that could inform us on the outcome of our participants, a follow-up study with longitudinal data on memory consolidation could be very useful.

Secondly, the neuroimaging approach we used in this paper only allowed us to make an indirect link between verbal long-term memory consolidation performance and brain structures. But as memory consolidation is believed to be a dynamic process, structural imaging may not be sufficient to capture difference between subgroups. Indeed, future research could add a combination of cognitive tasks with functional magnetic resonance imaging (fMRI) to further understand the processes at stake.

Thirdly, to measure episodic memory, we used a word-list task that is lacking ecological value. Although this task is the most commonly used to assess episodic memory in an experimental setting and is used as a proxy for everyday memory, we cannot be entirely certain that the processes at stake are the same inside and outside of the experimental setting. Future studies should focus on the development of more ecological measures to assess episodic memory in this population.

Fourthly, the size of our sample is acceptable for diagnostic group comparisons (22q11DS vs. typically developing controls) but both groups are not completely homogenous. For example, as mentioned before, the age range used in this paper is very large and developmental processes are difficult to capture in this setting. Once again, a follow-up study with longitudinal data could be very useful to disentangle the developmental dynamic of memory processes. Furthermore, even if it is a rare genetic disease, the phenotype of 22q11DS is very heterogeneous and research on this population tends to require a stratification of patients. Here we used a clustering method to stratify the sample. This had the consequence to reduce the sample size for the within

diagnostic group comparison and in the neuroimaging analyses and therefore decrease statistical power. This should be considered in the interpretation of our results.

Finally, there is a growing literature about the role of sleep on memory consolidation (e.g., Wilhelm, Prehn-Kristensen, & Born, 2012) that was not taken into account in this study. As sleep disturbances (e.g., sleep apnea) are more frequent in 22q11DS than in the normal population (Kennedy et al., 2014), the quality of sleep and the influence of sleep disturbances on long-term memory consolidation performance should be investigated.

5. Conclusion

In conclusion, this study tested the hypothesis of disrupted verbal long-term memory consolidation in 22q11DS and revealed the existence significant impairments compared to controls when delays longer than thirty minutes were examined. Furthermore, we characterized the heterogeneity of memory performance by dividing individuals with 22q11DS into subgroups by dividing into subgroups and identified a subgroup with low performance in memory recalls already at a delay of thirty minutes. This subgroup also had a significant reduction of volume in different hippocampal subfields and was associated with a more severe outcome (intellectual disability and higher disorganized psychotic symptoms). These results revealed different patterns of verbal long-term memory over time in the 22q11DS group, which should be considered in the development of cognitive intervention programs and for caregivers.

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Supplementary material

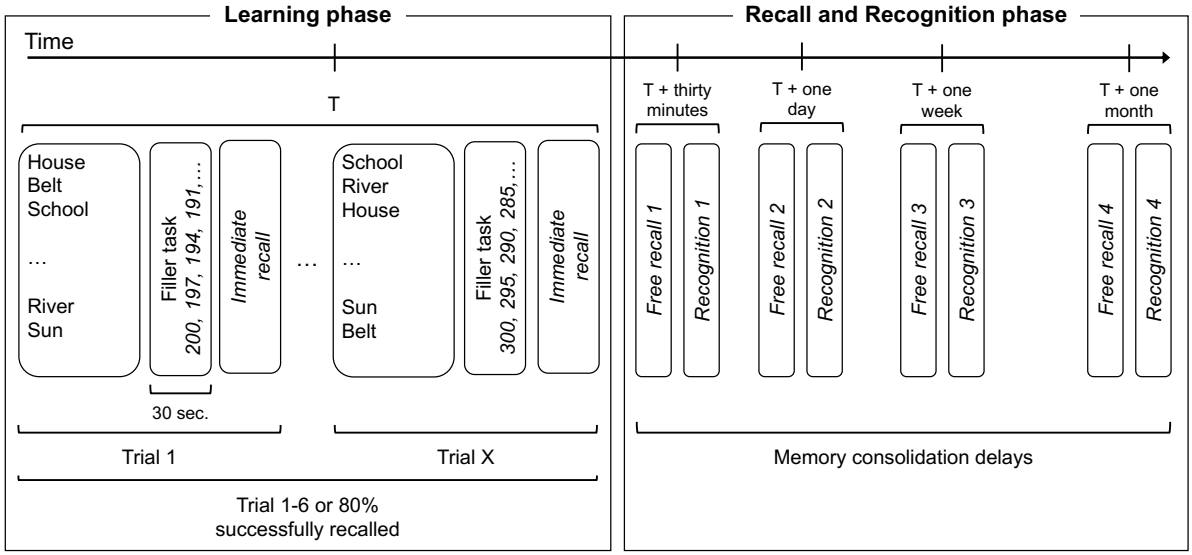

Figure S1: Displaying the different steps of the long-term episodic memory task.

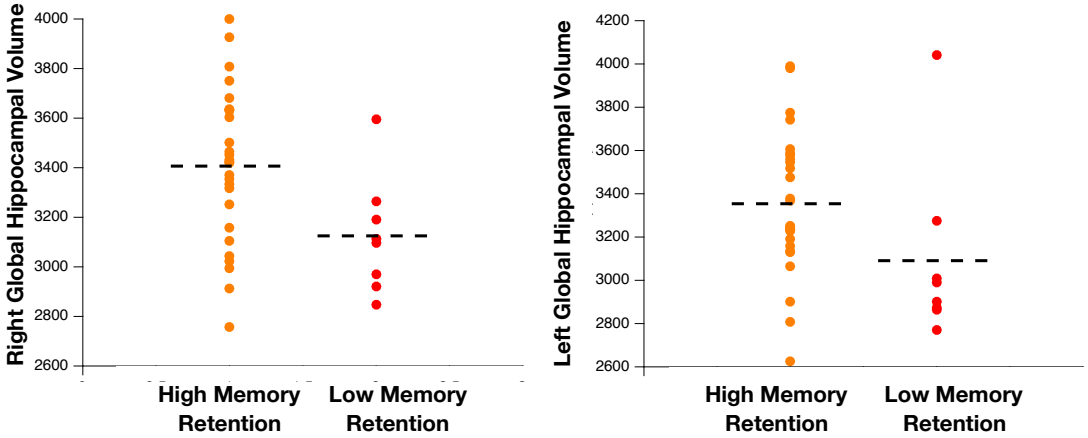

Figure S2: Values of right and left global hippocampal volume in individuals divided according to trajectories of normalized memory retention. Dashed lines indicate mean volume in each subgroup.

Table S1: Rey Auditory Verbal Learning Task (RAVLT), four parallel lists, in French/*English*:

List A	List B	List C	List D
Tambour/*Drum*	Pupitre/*Desk*	Orange/*Orange*	Violon/*Violin*
Rideau/*Curtain*	Berger/*Shepherd*	Fauteuil/*Chair*	Arbre/*Tree*
Ceinture/*Belt*	Moineau/*Sparrow*	Crapaud/*Toad*	Cravate/*Tie*
Café/*Coffee*	Soulier/*Shoe*	Bouchon/*Cork*	Jambon/*Ham*
École/*School*	Fourneau/*Stove*	Voiture/*Car*	Valise/*Suitcase*
Parent/*Parent*	Montagne/*Mountain*	Menton/*Chin*	Cousin/*Cousin*
Soleil/*Sun*	Lunette/*Glasses*	Rivage/*Shore*	Oreille/*Ear*
Jardin/*Garden*	Éponge/*Sponge*	Savon/*Soap*	Couteau/*Knife*
Casquette/*Cap*	Image/*Image*	Hôtel/*Hotel*	Escalier/*Stairs*
Paysan/*Farmer*	Bateau/*Boat*	Cheval/*Horse*	Chien/*Dog*
Moustache/*Moustache*	Mouton/*Sheep*	Insecte/*Insect*	Banane/*Banana*
Dindon/*Turkey*	Fusil/*Rifle*	Toilette/*Toilet*	Outil/*Tool*
Couleur/*Colour*	Crayon/*Pen*	Marmite/*Pot*	Chasseur/*Hunter*
Maison/*House*	Église/*Church*	Soldat/*Soldier*	Seau/*Bucket*
Rivière/*River*	Poisson/*Fish*	Serrure/*Lock*	Campagne/*Countryside*

Table S2: Recognition task example: List A, Recognition 1, in French/*English*:

Piano/*Piano*	Y	N	Tête/*Head*	Y	N
Tambour/*Drum*	Y	N	Jardin/*Garden*	Y	N
Tapis/*Carpet*	Y	N	Soleil/*Sun*	Y	N
Manteau/*Coat*	Y	N	Maçon/*Builder*	Y	N
Matin/*Morning*	Y	N	Bouche/*Mouth*	Y	N
Rideau/*Curtain*	Y	N	Casquette/*Cap*	Y	N
Frère/*Brother*	Y	N	Oiseau/*Bird*	Y	N
École/*School*	Y	N	Paysan/*Farmer*	Y	N
Plage/*Beach*	Y	N	Lueur/*Glow*	Y	N
Punition/*Punishment*	Y	N	Parent/*Parent*	Y	N
Ceinture/*Belt*	Y	N	Moustache/*Moustache*	Y	N
Maison/*House*	Y	N	Chambre/*Room*	Y	N
Sapin/*Fir*	Y	N	Dindon/*Turkey*	Y	N
Café/*Coffee*	Y	N	Eau/*Water*	Y	N
Rivière/*River*	Y	N	Couleur/*Colour*	Y	N

NB: target words are underlined and the correct answer (Yes/No) is marked in grey.

Table S3: Examples of phonemic and semantic distractors from the recognition part of the task, in French/*English*:

Target word	**Phonemic distractor**	**Semantic distractor**
Banane/*Banana*	Cabane/*Hut*	Poire/*Pear*
Soldat/*River*	Panda/*Panda*	Guerre/*War*
Bouchon/*Cork*	Balluchon/*Bundle*	Couvercle/*Lid*