UNIVERSITÉ DU QUÉBEC À MONTRÉAL

INFLUENCE DES NEUROLEPTIQUES SUR LES FONCTIONS COGNITIVES ET LA SYMPTOMATOLOGIE DE PERSONNES SCHIZOPHRÈNES

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LISTE DES ABRÉVIATIONS

$5HT_2$	Récepteurs sérotoninergiques de type 2
ANOVA	Analysis of Variance
CPT	Continuous Performance Test
CVLT	California Verbal Learning Test
CVTT	Computed Visual Tracking Task
D_2	Récepteurs dopaminergiques de type 2
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual
ESRS	Extrapyramidal Symptoms Rating Scale
HD	Huntington disease
HVLT	Hopkins Verbal Leaning Test
IRMf	Imagerie par Résonance Magnétique fonctionnelle
NLP	Neuroleptique
PANSS	Positive and Negative Syndrome Scale
PD	Parkinson's disease
PFC	Prefrontal cortex
PL	Procedural learning
PLT	computer-controlled Procedural Learning Tester
SEP	Symptômes extrapyramidaux
SZ / SC	Schizophrénie
TEP	Tomographie par émission de positrons
WCST	Wisconsin Card Sorting Test

RÉSUMÉ GÉNÉRAL

Il est reconnu que les patients schizophrènes montrent des dysfonctions cognitives qui affectent principalement l'attention, la mémoire et les fonctions exécutives. Depuis l'arrivée des neuroleptiques (NLPs) atypiques, de nombreux chercheurs se sont penchés sur l'effet de ces traitements sur la performance cognitive de patients schizophrènes comparé aux traitements NLPs typiques. À ce jour, les études évaluatives concernant l'efficacité des NLPs montrent des résultats non homogènes. L'absence de groupe contrôle ou d'assignation randomisée en double-aveugle, la focalisation sur un aspect spécifique du fonctionnement cognitif sur le court terme, ou l'absence d'évaluation des effets des médications concomitantes sur les performances cognitives explique principalement les divergences dans les résultats de ces études. Les trois articles proposés dans le cadre de cette thèse visent à préciser les effets à long terme des NLPs typiques et atypiques sur l'attention, la mémoire épisodique verbale, l'apprentissage procédural et les fonctions exécutives de patients schizophrènes en prenant en compte l'ensemble de ces variables cliniques et méthodologiques. Les performances cognitives d'un groupe de patients schizophrènes traités avec un NLP atypique, la rispéridone, et d'un groupe de patients schizophrènes traités avec un NLP typique, l'halopéridol, ont été comparées à celle d'un groupe contrôle lors de tâches cognitives administrées à 0, 3, 6 et 12 mois. Dans l'ensemble, la rispéridone ne montre pas d'effet supérieur à l'halopéridol sur les fonctions cognitives mettant à contribution les systèmes dopaminergiques méso-cortico-limbiques. Cependant, la rispéridone montre un effet thérapeutique supérieur pour ce qui est de la réduction des symptômes négatifs, ainsi que de meilleures performances que sous traitement halopéridol lors de tâches d'apprentissage procédural. Les généralisations des travaux antérieurs sur les effets des neuroleptiques typiques et atypiques, qui n'avaient pas pris en compte d'évaluer les performances cognitives de patients à celles de sujets contrôles sains, sont limitées dans leur portée et posent problème. Il en va de même avec les travaux qui n'ont étudié que les effets d'une seule drogue à la fois ou l'effet à court terme de ces traitements. Les chercheurs qui se penchent sur les effets des NLPs sur les fonctions cognitives doivent prendre en compte ces facteurs méthodologiques non négligeables afin de tirer des conclusions plus justes.

Mots clés : apprentissage procédural, attention, dopamine, fonctions exécutives, lecture en miroir, mémoire verbale, neuroleptique, schizophrénie, symptômes extrapyramidaux, symptômes négatifs, symptômes positifs.

CHAPITRE I

CONTEXTE THÉORIQUE

INTRODUCTION

La schizophrénie (SZ) est considérée comme un trouble psychiatrique chronique et invalidant. La prévalence de la SZ est généralement estimée à 1% (Lewis & Lieberman, 2000). Les premiers signes apparaissent souvent à l'adolescence ou vers le début de l'âge adulte. Bien que la fréquence du trouble soit la même selon le sexe, l'apparition des symptômes est plus précoce chez les hommes (Lewis & Lieberman, 2000). On ne connaît pas encore l'étiologie de la SZ.

L'évolution de ce trouble est caractérisé par des symptômes positifs (hallucinations, délires, altération du cours de la pensée, comportements incompréhensibles, hostilité) ou négatifs (anhédonie et retrait social, alogie, apathie, émoussement des affects, inattention). Une fois les premiers symptômes manifestés, le trouble devient chronique avec récurrence d'épisodes psychotiques aigus. Les symptômes deviennent plus stables environ cinq à 10 ans après l'apparition des premières manifestations (Lewis & Lieberman, 2000). Le diagnostic de SZ selon le *Manuel Diagnostic et Statistique des Troubles Mentaux* (DSM IV; American Psychiatric Association, 1996) repose sur la présence d'au moins deux des symptômes suivants, à savoir les délires, hallucinations, discours incohérent, un comportement très désorganisé ou catatonie, ou des symptômes négatifs. De plus, il faut qu'un dysfonctionnement social et de comportement soit remarqué et qu'il y ait eu des signes de trouble mental pendant au moins six mois. Les troubles psychotiques dus à une condition médicale ou induits par une substance sont exclus. Un trouble schizo-affectif ou un trouble de l'humeur constituent d'autres critères d'exclusion.

Outre les signes cliniques, les personnes diagnostiquées schizophrènes présentent un éventail de dysfonctions cognitives, tels que des troubles exécutifs, psychomoteurs, d'attention, d'apprentissage ou de mémoire (Gold & Harvey, 1993; Heinrichs & Zakzanis, 1998; Kasper & Resinger, 2003; Kurtz, 2005). La performance des patients schizophrènes aux tests neuropsychologiques est généralement inférieure à celle de sujets contrôles sains (Keefe, 1995; Saykin et al., 1991). On rapporte qu'environ 75 % des patients schizophrènes présentent des troubles cognitifs (e.g., Palmer et al, 1997). Des différences dans les profils de performance cognitive peuvent relever de l'hétérogénéité du diagnostic de la schizophrénie (Mortimer, 2008). En effet, les cinq sous-types de la schizophrénie dans le DSM-IV (catatonique, paranoïde, désorganisé, indifférencié, résiduel) mettent en évidence le caractère hétérogène de cette maladie.

1.1 Hypothèses biochimiques de la schizophrénie

D'après la théorie dopaminergique proposée par Weinberger (1987), la SZ résulterait d'une altération fonctionnelle des projections dopaminergiques. Ainsi, l'expression des symptômes positifs serait la conséquence d'une hyperdopaminergie mésolimbique tandis que l'existence d'une hypoactivité dopaminergique mésocorticale expliquerait les symptômes négatifs et de certains déficits cognitifs. L'apparition de symptômes psychotiques chez le sujet sain et l'exacerbation des symptômes positifs chez les patients schizophrènes suivant la prise de drogues amphétaminiques (qui agissent en tant qu'agonistes dopaminergiques) constituent une évidence indirecte qui appuierait l'hypothèse dopaminergique de la SZ.

La dopamine est essentiellement produite par deux structures cérébrales mésencéphaliques: l'aire tegmentale ventrale et la partie compacte de la substance noire. Divers circuits utilisant la dopamine ont été identifiés. Cependant, seulement trois d'entre eux seront abordés, car ils constituent les principales voies

dopaminergiques impliquées dans la physiopathologie de la SZ ainsi que dans les effets thérapeutiques et toxiques des neuroleptiques (NLPs).

Bien que les récepteurs dopaminergiques D_2 soient la pierre angulaire de la physiopathologie de la SZ, d'autres neurotransmetteurs sont également impliqués tels le glutamate, le GABA et la noradrénaline (Kinon & Lieberman, 1996; Reynolds, 2008). Ces derniers ne seront toutefois pas traités dans les études présentées dans cette thèse car les NLPs agissent essentiellement sur les systèmes dopaminergiques.

1.2 Voie mésolimbique

Le système mésolimbique relie l'aire tegmentale ventrale à plusieurs structures du système limbique, dont le noyau accumbens, les noyaux du septum latéral, l'hippocampe et l'amygdale. Cette voie intervient, entre autres, dans l'adaptation des comportements émotionnels, dans la régulation des émotions et dans le contrôle de la motivation. L'hyperactivité de ce circuit expliquerait la manifestation des troubles de la pensée, des idées délirantes et des hallucinations chez le patient schizophrène. Or, l'affinité des NLPs pour les récepteurs D_2 mésolimbique sous-tendrait l'effet thérapeutique recherché, c'est-à-dire le traitement des psychoses (Stahl, 2002).

1.3 Voie mésocorticale

Le circuit mésocortical origine de l'aire tegmentale ventrale et ses neurones dopaminergiques projettent principalement vers le cortex préfrontal, cingulaire et périrhinal. Sur le plan cognitif, cette voie serait essentiellement impliquée dans les processus attentionnels, les fonctions exécutives et la mémoire de travail (Floresco & Magyar, 2006). L'activité hypodopaminergique du système mésocortical expliquerait les déficits cognitifs mis en évidences dans la schizophrénie et sous-tendrait les symptômes négatifs relatifs à cette maladie.

1.4 Voie nigrostriée

Les neurones du système nigrostrié proviennent de la partie compacte de la substance noire et projettent essentiellement dans le striatum dorsal (noyau caudé et putamen). Cette voie serait impliquée dans la facilitation et l'initiation du mouvement volontaire, ainsi que dans l'automatisation des procédures motrices ou cognitives. L'action antagoniste des NLPs classiques sur les récepteurs dopaminergiques D_2 nigrostriataux induit des effets secondaires, tels que les symptômes extrapyramidaux (SEPs; Kapur, Zipursky, Jones, Remington & Houle, 2000). Ces derniers apparaissent généralement lorsque le taux de blocage ou d'occupation des récepteurs D_2 du striatum dépasse 80%. La dystonie aiguë, le syndrome parkinsonien (visage figé, bradykinésie, rigidité musculaire, tremblements au repos), l'akathisie, le tremblement périoral et les dyskinésies tardives sont les SEPs observés chez les patients schizophrènes traités aux NLPs (Casey, 1997; Pierre, 2005). L'halopéridol est reconnu comme prototype des NLPs classiques ou typiques. Les NLPs atypiques tels que la clozapine, l'olanzapine, la ziprasidone et la rispéridone, agissent simultanément en tant qu'agent antagoniste des récepteurs dopaminergiques et sérotoninergiques (5HT) du système mésolimbique et mésocortical (Meltzer & McGurk, 1999). Toutefois, leur affinité pour les récepteurs sérotoninergiques $5HT_{2A}$ est supérieure à celle des récepteurs dopaminergiques D_2. À des doses thérapeutiques, les NLPs atypiques auraient un plus faible taux d'occupation des récepteurs D_2 striataux et provoqueraient moins de SEPs (Farde et al., 1992; Kapur et al., 2000). Par exemple, la rispéridone est un NLP atypique qui exerce ses effets thérapeutiques par le blocage simultané des récepteurs D_2 et $5HT_{2A}$. Cependant, à des doses supérieures à 6mg par jour, son affinité pour les récepteurs D_2 s'accroît et la rispéridone perd alors ses propriétés atypiques entrainant des effets secondaires extrapyramidaux comparables aux NLPs classiques. En effet, Kapur, Remington, Zipursky, Wilson et Houle (1995) ont déterminé à l'aide d'imagerie tomographique d'émission par positrons (TEP) le taux d'occupation dopaminergique striatal sous 2mg, 4mg et 6mg de risperidone. Ces doses de NLP correspondraient à

un taux d'occupation des récepteurs D_2 du striatum de 66%, 73% et 79%, respectivement.

Les NLPs atypiques sont également associés à une diminution des symptômes négatifs et des dysfonctions cognitives (Meltzer & McGurk, 1999). Or, l'action antagoniste des récepteurs $5HT_2$ à la sérotonine qui caractérise les NLPs atypiques augmenterait l'activité dopaminergique des lobes frontaux. En effet, Pehek (1996) a montré que les antagonistes $5HT_{2A}$ favorisent la libération de dopamine dans le cortex préfrontal.

Dans l'ensemble, le blocage dopaminergique D_2 de la voie mésolimbique — qui serait hyperactive dans la SZ — constitue l'effet thérapeutique cible du traitement des symptômes positifs. Cependant, l'action antagoniste D_2 des NLPs classiques ne bloque pas uniquement les récepteurs D_2 de la voie mésolimbique. Au niveau de la voie mésocorticale — qui serait déjà hypoactive dans la SZ — le blocage D_2 pourrait donc exacerber les symptômes négatifs et certains déficits cognitifs. Enfin, le blocage D_2 de la voie nigrostriée induit les SEPs. Or, les NLPs atypiques se distinguent des classiques par leur propriété antagoniste sérotoninergique 5HT2. La réduction des symptômes négatifs et l'amélioration des fonctions cognitives reposeraient sur l'action de cette propriété pharmacologique sur les voies mésocorticales et nigrostriées. Normalement, la sérotonine inhibe la libération de dopamine. Il semblerait alors que le blocage des récepteurs sérotoninergiques par les NLPs atypiques favorise la libération de dopamine au niveau mésocortical et nigrostrié.

1.5 Médication neuroleptique et fonctionnement cognitif

Si dans le passé on s'est intéressé aux effets thérapeutiques des NLPs atypiques et typiques, aujourd'hui on s'intéresse davantage à l'action de ces traitements sur le fonctionnement cognitif. Comprendre l'impact de ces drogues sur la cognition est de

première importance : la performance cognitive constitue un bon index de réinsertion sociale et d'adaptation du patient à la vie de tous les jours (Green, 1996; Hofer et al., 2005; Velligan et al., 1997).

Plusieurs études qui ont porté sur l'effet des NLPs typiques et atypiques rapportent une amélioration des fonctions cognitives suite à un traitement aux NLPs atypiques (Cuesta, Peralta & Zarzuela, 2001; Green et al., 1997; Harvey, Green, McGurk & Meltzer, 2003; Keefe, Silva, Perkins & Lieberman, 1999; Kern et al., 1999; Meltzer & McGurk, 1999; Purdon, Labelle & Boulay, 2001; Rossi et al., 1997; Sax, Strakowski & Keck, 1998). Par exemple, Harvey, Green, McGurk et Meltzer (2003) ont étudié les effets de la rispéridone et de l'olanzapine, deux NLPs atypiques, sur l'attention, la mémoire de travail, les fonctions exécutives, la fluidité et la mémoire verbale. Les participants schizophrènes (N=377) ont été suivis sur une période de 8 semaines. Les résultats montrent que ces deux NLPs atypiques améliorent l'ensemble des fonctions cognitives évaluées. Cependant, cette étude présente deux problèmes. D'une part, il n'y a pas de comparaison sous traitement NLP typique ni de comparaison à un groupe contrôle constitué de participants sains, d'autre part. Une autre étude réalisée par Velligan et al. (2002) compare l'effet de la quetiapine (atypique) et de l'halopéridol (typique) sur une période de six mois. Leurs résultats révèlent que les performances aux tests de fonction exécutive et de mémoire verbale étaient supérieures pour le groupe sous traitement atypique.

Bien qu'il existe plusieurs études dont les résultats vont dans le sens d'une supériorité des NLPs atypiques sur le fonctionnement cognitif de patients schizophrènes, certains travaux obtiennent des résultats contradictoires (Hoff et al., 1996; Lee, Jayathilake & Meltzer, 1999; Purdon et al., 2000). Par exemple, Sumiyoshi, Jayathilake et Meltzer (2002) ont évalué l'efficacité de la melperone, un NLP atypique, sur le fonctionnement cognitif de schizophrènes durant six semaines

et n'ont montré aucun changement aux tests de mémoire et de fluidité verbale, d'attention soutenue ou de mémoire de travail. Cette étude réalisée sur une courte période ne comportait pas non plus un groupe de comparaison sain. Purdon et al. (2000) ont évalué les effets de l'olanzapine et la rispéridone (NLPs atypiques) ainsi que du halopéridol sur les habiletés psychomotrices, la mémoire verbale et non-verbale, l'attention et les fonctions exécutives. Le suivi sur 12 mois a montré une efficacité supérieure de l'olanzapine sur l'ensemble des performances cognitives; aucune différence n'a été observée entre les groupes traités à l'halopéridol ou à la rispéridone.

Plusieurs travaux ont aussi porté sur la relation entre les déficits cognitifs et la sévérité des symptômes schizophréniques. Ainsi, il existerait une association entre les symptômes négatifs et une performance faible au test du Wisconsin Card Sorting Test (WCST, Berg, 1948; Basso, Nasrallah, Olson & Bornstein, 1998; Berman et al., 1997; Heydebrand et al., 2004; Voruganti, Heslegrave & Award, 1997). D'autres auteurs ont montré qu'une réduction des symptômes positifs était associée à une amélioration des performances cognitives (Hoff et al., 1999; Ritter, Meador-Woodruff & Dalack, 2004). Toutefois, la relation entre la symptomatologie et le fonctionnement cognitif de personnes atteintes de SZ n'est pas claire, puisque plusieurs études obtiennent des résultats divergents (par ex., Collins, Remington, Coulter & Birkett, 1997; Hughes et al., 2002).

1.5.1 Attention

L'attention sélective, une fonction cognitive essentielle aux activités de la vie quotidienne, fait partie des troubles cognitifs les plus fréquemment rapportés chez les personnes atteintes de SZ. En effet, les patients schizophrènes éprouvent des difficultés à maintenir un niveau de vigilance nécessaire à la réalisation de tâches qui impliquent la sélection de stimuli visuels (Rossi et al., 1997; Stip & Lussier, 1996) et

auditifs pertinents (Green et al., 1997; Rossi et al., 1997). Selon plusieurs auteurs, une diminution de la dopamine dans le cortex préfrontal serait responsable des déficits d'attention associés à la SZ (Cohen & Servan-Schreiber,1992; Goldman-Rakik, 1994; Vendrell et al., 1995). De nombreuses observations reflètent l'implication des aires préfrontales et du gyrus cingulaire dans le processus de l'attention. Barch et al. (2001) ont montré à l'aide d'une étude IRMf auprès de jeunes patients schizophrènes qui n'avaient pas encore reçu de médication, une diminution de l'activation de l'aire préfrontale dorsolatérale durant une tâche d'attention soutenue, le Continuous Performance Test (CPT; Rosvold, Mirsky, Sarason, Bransome & Beck, 1956). Une étude similaire conduite par Volz et al. (1999) montre aussi une diminution de l'activité du cortex préfrontal médian droit, du gyrus cingulaire droit et du thalamus gauche de patients schizophrènes durant une tâche adaptée du CPT comparativement au groupe contrôle. Une réduction de l'activité du gyrus cingulaire antérieur a aussi été rapportée chez les patients schizophrènes durant une tâche de discrimination auditive (Holcomb et al., 2000).

Un ralentissement dans la vitesse de traitement de l'information est également rapporté chez ces patients (par ex., Stip & Lussier, 1996). Des études auprès de patients schizophrènes qui n'ont jamais reçu de médication révèlent un déficit de l'attention ainsi qu'un ralentissement psychomoteur comparativement à la performance d'un groupe contrôle (Hong et al., 2002). Certains auteurs avancent que les NLPs atypiques permettraient d'améliorer la performance des personnes schizophrènes aux tests d'attention ainsi que leur temps de réponse (Green et al., 1997; Sharma & Mockler, 1998). Selon eux, l'augmentation de l'activité dopaminergique du cortex préfrontal alliée à la diminution des SEPs seraient responsables de cette supériorité des NLPs atypiques (Harvey, Moriarty, Serper, Schnur & Lieber, 2000; Lee, Jayathilake & Meltzer, 1999; McGurk, Lee, Jayathilake & Meltzer, 2004; Velligan et al., 2002). Cependant, d'autres études n'ont pas montré

cette supériorité des NLPs atypiques (Hong et al., 2002; Lindenmayer et al. 1998). Selon Liu, Chen, Chang et Lin (2000), les déficits d'attention restent relativement stables tout au long du traitement, peu importe la médication.

1.5.2 Fonctions exécutives

Des anomalies fonctionnelles, telle une diminution du débit sanguin cérébral dans le cortex préfrontal, ont été observées chez les patients schizophrènes (Harvey et al., 1999; Ritter, Meador-Woodruff & Dalack, 2004; Saykin et al., 1994). Par ailleurs, un déficit des fonctions exécutives, tel qu'évalué par le WCST est fréquemment rapporté auprès de cette population. Des études en imagerie cérébrale auprès de personnes saines ont montré une activation du cortex préfrontal dorsolatéral durant la tâche du WCST (Berman et al., 1995; Marenco, Coppola, Daniel, Zigun & Weinberger, 1993). Chez le schizophrène, l'activation de l'aire préfrontale dorsolatérale n'est pas observée durant cette même tâche (Weinberger, Berman & Zec, 1986), ce qui suggère l'existence d'une hypoactivité de cette région cérébrale dans la SZ.

Les fonctions exécutives sont impliquées dans les processus mentaux tels que l'initiation de stratégies, la flexibilité cognitive, l'inhibition, la planification, la réalisation et le contrôle de toute action volontaire (motrice ou cognitive) dirigé vers un but précis et nécessitant un niveau élevé d'intégration. Or, ces fonctions sont primordiales dans l'adaptation à une situation nouvelle ou lors de la réalisation de tâches complexes. Green, Kern, Braff et Mintz (2000) ont montré que la performance au WCST serait un bon prédicteur du fonctionnement de personnes schizophrènes dans la communauté. De plus, McGurk et Meltzer (2000) on montré que les personnes schizophrènes qui exercent un emploi, comparées à celles qui ne travaillent pas, ont aussi une meilleure performance au WCST.

Divers auteurs ont suggéré que le mécanisme d'action des NLPs atypiques au niveau du système dopaminergique mésocortical, permettrait d'améliorer les fonctions exécutives qui relèvent du cortex frontal et préfrontal. Ainsi, Sumiyoshi, Jayathilake et Mletzer (2002) ont évalué l'effet d'un traitement NLP atypique (melperone) sur les performances cognitives de 19 schizophrènes. Après 6 semaines, les résultats montrent une amélioration des fonctions exécutives, telles qu'évaluées par le WCST. Cuesta et al. (2001) ont étudié les effets différentiels de la clozapine, de la rispéridone et d'un NLP conventionnel sur plusieurs fonctions cognitives de personnes schizophrènes. Après 6 mois de traitement, les schizophrènes traités à la rispéridone ont montré une meilleure performance au test du WCST que ceux traités à l'olanzapine ou médication conventionnelle. D'autres auteurs ont également observé une amélioration des fonctions exécutives suivant un traitement atypique, telles qu'évaluées par le WCST (Rossi et al., 1997) et le Trail Making B (McGurk et al., 1997). Toutefois, certaines études n'ont pas montré cette supériorité des NLPs atypiques sur l'amélioration des dysfonctions exécutives (Buchanan, Holstein & Breier, 1994; Daniel et al., 1996; Hoff et al., 1996). Lee, Jayathilake et Meltzer (1999), par exemple, n'ont observé aucune amélioration de la performance au WCST à la suite d'un traitement atypique (clozapine) ou d'un traitement conventionnel sur une période de 12 mois. Des résultats similaires ont été rapportés suite à une étude menée par Purdon et al. (2000). Les résultats ne montrent aucune différence entre la rispéridone et l'halopéridol dans l'amélioration des habiletés exécutives, telles qu'évaluées par le WCST. Lors d'une étude à court terme, les participants schizophrènes qui ont passé d'un traitement typique à un traitement atypique (clozapine), ne montrent aucune amélioration de leur performance au WCST après 3 mois de médication atypique (Hoff et al., 1996).

1.5.3 Mémoire verbale

L'intérêt de la recherche sur la mémoire verbale des schizophrènes provient, entre autre, des études en imagerie cérébrale et post-mortem qui ont montré des

anomalies neuroanatomiques au niveau du cortex temporolimbique gauche (Barta, Pearlson, Powers, Richards & Tune, 1990; Keshavan et al., 1998). L'évaluation de la performance cognitive de schizophrènes à une tâche de mémoire épisodique verbale – le California Verbal Learning Test (CVLT; Delis, kramer, Kaplan & Ober, 1987) – montre des troubles de rappel libre à court et long terme (Hill, Beers, Kmiec, Keshavan & Sweeney, 2004). Une incapacité à organiser le contenu d'une liste de mots selon une stratégie sémantique serait en partie responsable des troubles de mémoire verbale des schizophrènes (Hill et al., 2004). Cette stratégie a d'ailleurs été associée aux activités de l'aire préfrontale gauche chez des participants sains, durant la tâche du CVLT (Savage et al., 2001). L'ensemble de ces observations suggère que le CVLT sollicite à la fois les aires temporales et préfrontales. En effet, Ragland et al. (2003) ont montré, à l'aide d'imagerie cérébrale, une réduction de l'activité frontotemporale de schizophrènes durant une tâche d'encodage verbale. Or, il a été proposé que l'action pharmacologique différentielle des NLPs typiques et atypiques sur les régions méso-cortico-limbiques puisse expliquer l'effet bénéfique des NLPs atypiques à des tâches de mémoire épisodique.

Il est maintenant connu que les traitements anticholinergiques, donnés conjointement au traitement NLPs typiques (afin de réduire les symptômes parkinsonniens) affectent la mémoire des schizophrènes (Blanchard & Neale, 1992; Frith, 1984). Ainsi, contrairement au traitement conventionnel, certains NLPs atypiques montrent une amélioration de la performance des personnes atteintes de SZ à des tâches de mémoire verbale (Bilder et al., 2002; Cuesta et al., 2001; Kasper & Resinger, 2003). Toutefois, il s'avère que ce n'est pas tous les NLPs atypiques qui aient cette propriété. En effet, Bilder et al. (2002) n'ont pas montré de différence entre le traitement atypique (clozapine) et le traitement conventionnel (halopéridol) sur les performances obtenues au Hopkins Verbal Learning Test (HVLT; Brantd, 1991). Dans cette étude, la rispéridone s'est avérée un traitement NLP supérieur. Les

auteurs notent que la clozapine possède des propriétés anticholinergiques intrinsèques très élevées, ce qui pourrait expliquer que ce NLP atypique ne soit pas supérieur au traitement conventionnel. Brébion, Bressan, Amador, Malaspina et Gorman (2004) ont montré que les troubles de la mémoire verbale sont associés au traitement anticholinergique, indépendamment du type de traitement NLP.

1.5.4 Apprentissage procédural

La mémoire procédurale (ou implicite) est la capacité à acquérir des habiletés sensori-motrices ou cognitives par la pratique et dont l'apprentissage conduit à une automatisation de la tâche (Cohen & Squire, 1980). Contrairement à l'apprentissage procédural, la mémoire déclarative (ou explicite) nécessite un effort conscient de récupération.

Des observations cliniques laissent présumer une dissociation entre la mémoire procédurale et déclarative. En effet, les personnes atteintes de pathologies neurologiques qui affectent le fonctionnement normal du striatum, tels que la maladie de Huntington et la maladie de Parkinson échouent des tâches associées à l'apprentissage procédural mais pas celles associées à la mémoire déclarative (Harrington, Haaland, Yeo & Marden, 1990). À l'inverse, les gens atteints d'amnésie montrent une performance intacte aux tâches de mémoire procédurale, mais échouent les tâches de mémoire déclarative (Squire, 1987). Ainsi, les noyaux gris centraux, plus spécifiquement le striatum, seraient essentiels au processus d'apprentissage procédural (Reber & Squire, 1999).

Les conclusions tirées des études sur l'apprentissage procédural auprès de personnes schizophrènes ne sont pas claires. Beaucoup de travaux ont rapporté une mémoire procédurale intacte chez les schizophrènes, telle qu'évaluée par le test de la Tour de Toronto (Gras-Vincendon et al., 1994), le test du dessin en miroir (Takano et

al., 2002), la tâche de poursuite rotative (Clare, McKenna, Mortimer & Baddeley, 1993) et la lecture en miroir (Clare et al, 1993; Takano et al., 2002). D'autres n'ont pas corroboré ces observations et ont montré un déficit d'apprentissage procédural tel que mesuré par la tour d'Hanoï (Gimenèze et al., 2003) ou la tâche de poursuite rotative (Schwartz, Rosse, Veazey & Deutsch, 1996).

La plupart des études précédentes n'ont pas fait la distinction entre les NLPs typiques et atypiques. Lorsque cette distinction est prise en considération, le taux de SEP induit par les NLPs à forte affinité dopaminergique D_2 nigrostriatal est associé à la sévérité des déficits d'apprentissage procédural (Granholm, Bartzokis, Asarnow & Marder, 1993). Les personnes schizophrènes traités par un NLP typique montrent une performance significativement plus faible au test du dessin en miroir comparativement à ceux qui reçoivent un traitement atypique (Bédard, Schérer, Delorimier, Stip & Lalonde, 1996; Bédard et al., 2000). Des résultats similaires ont été obtenus à l'aide du CVTT (Computed Visual Tracking Task; Willingham, Hollier & Joseph, 1995). Contrairement au traitement NLP typique, une meilleure performance a été observée chez les schizophrènes traités aux NLPs atypiques (Paquet et al., 2004).

À ce jour, très peu de travaux ont évalué l'effet à long terme des NLPs typiques et atypiques sur l'apprentissage procédural. La plupart des études sont réalisées sur une très courte période ou sur une seule évaluation. Lorsque les effets des NLPs sont étudiés sur une période à moyen terme, la performance à une tâche d'apprentissage procédural dépend des propriétés pharmacologiques de chacun des traitements utilisés. Ainsi, après 6 semaines, l'apprentissage des essais de la Tour de Toronto était préservé pour les trois groupes de NLPs à l'étude : rispéridone, olanzapine et halopéridol. Cependant, l'halopéridol et la rispéridone, mais pas l'olanzapine, ont

montré une diminution substantielle des performances après 6 mois de traitement (Purdon, Woodward & Lindborg, 2003). Les auteurs de cette étude concluent que le pourcentage de liaison dopaminergique du striatum serait similaire entre l'halopéridol et la rispéridone, ce qui explique en partie que deux NLPs atypiques (rispéridone et olanzapine) diffèrent quant aux effets obtenus à ce test d'apprentissage procédural.

Dans l'ensemble, cette revue de littérature permet de constater que certains aspects méthodologiques limitent les conclusions que l'on peut tirer des études sur les NLPs et leur influence sur le fonctionnement cognitif. D'une part, les divers résultats peuvent être expliqués par l'hétérogénéité des participants (âge, durée de la maladie) et les types de médication employés. D'autre part, l'évaluation à très court terme des effets de la médication sur le fonctionnement cognitif et l'absence d'un groupe contrôle constitué de participants sains contribuent aussi aux divergences rapportées.

CHAPITRE II

HYPOTHÈSES

Les travaux poursuivis dans le cadre de cette thèse visent à préciser les effets à long terme de deux classes de NLPs, typique (halopéridol) et atypique (rispéridone), sur les fonctions cognitives de patients schizophrènes et de comparer la performance des sujets atteints de SZ à celle d'un groupe contrôle sain. Les études présentées ici visent à vérifier les hypothèses suivantes :

2.1 Hypothèses

1) Prenant en compte la disparité des profils pharmacologiques des NLPs typiques et atypiques, les patients schizophrènes traités à la rispéridone (un NLP atypique ayant une affinité pour les récepteurs sérotoninergiques $5HT_{2A}$ supérieure à celle des récepteurs dopaminergiques D_2) montreront une meilleure amélioration des symptômes négatifs que ceux traités au halopéridol (un NLP classique à forte affinité pour les récepteurs dopaminergiques D_2).

2) Si la présence d'une hypodopaminergie frontale dans la schizophrénie explique la manifestation des symptômes négatifs et les dysfonctions cognitives sous-jacentes au cortex préfrontal, une amélioration des symptômes négatifs sera associée à une amélioration des performances cognitives qui dépendent de l'intégrité des régions cérébrales frontales.

3) Les patients schizophrènes traités avec la rispéridone montreront une performance supérieure à celle des patients traités avec l'halopéridol à des tâches cognitives mettant à contribution le système dopaminergique méso-cortico-limbique, particulièrement le cortex préfrontal. Étant donné que les patients schizophrènes se caractérisent par une dysfonction frontale, ceux-ci présenteront une performance cognitive plus faible à celle des sujets contrôles sains.

4) Considérant la forte affinité des NLPs classiques pour les récepteurs dopaminergiques D_2 du système nigrostrié, les patients schizophrènes traités avec l'halopéridol montreront un apprentissage procédural inférieur à ceux des patients traités avec la rispéridone et à des sujets sains lors d'une tâche de lecture en miroir.

CHAPITRE III

METHODOLOGIE

3.1 Participants

Tous les patients schizophrènes qui ont participé à cette étude ont d'abord été traités par un NLP typique (halopéridol). Ils ont ensuite été répartis aléatoirement en deux groupes de traitements NLPs : la moitié ont poursuivi le traitement typique tandis que les autres ont reçu un traitement atypique (rispéridone). Les schizophrènes sélectionnés pour un traitement à la rispéridone ont subi une réduction graduelle de leur dose de NLP typique de 25% à chaque semaine ainsi qu'une titration progressive de rispéridone de 0.5 mg BID, 1 mg BID, 1.5 mg BID et 2 mg BID (la majorité ont atteint une dose stable de NLP atypique après 4 semaines). Cette étude d'une durée de 12 mois a été menée en double-aveugle. Ainsi, l'expérimentateur ignorait quel était le type de traitement NLP des participants rencontrés pour l'administration des tâches cognitives et le clinicien, responsable d'évaluer la symptomatologie et les effets extrapyramidaux, ignorait les performances cognitives des participants. Un groupe contrôle de personnes saines a été recruté en tenant compte de l'âge et du niveau d'éducation des patients schizophrènes. Tous les participants sont exempts de troubles susceptibles d'influencer leurs fonctions cognitives (atteinte cérébrale, consommation abusive de drogues ou d'alcool, dépression, démence).

3.2 Epreuves d'évaluation

Les diverses fonctions cognitives (mémoire verbale, apprentissage procédural, fonctions exécutives et attention) ont été évaluées à l'aide d'une batterie de tests neuropsychologiques administrée à 4 occasions sur une période de 12 mois (0, 3, 6 et 12 mois). Des échelles cliniques ont été administrées auprès des participants afin

d'évaluer leur niveau de psychopathologie et la sévérité des effets secondaires extrapyramidaux à travers le temps.

3.2.1 Evaluation clinique

3.2.1.1 Symptômes psychopathologiques

Le *Positive and Negative Syndrome Scale* (PANSS; Kay, Fiszbein & Opler, 1987) est une échelle d'évaluation qui permet de déterminer le profil psychopathologique de la SZ. Cette échelle permet de calculer les scores de 3 dimensions : les symptômes positifs, les symptômes négatifs et la psychopathologie générale.

3.2.1.2 Symptômes extrapyramidaux

La sévérité des manifestations indésirables de type extrapyramidal a été évaluée à l'aide de l'ESRS (Extrapyramidal Symptom Rating Scale; Chouinard, Ross-Chouinard, Annable & Jones, 1980). Cette échelle permet de calculer les scores de 7 catégories associés aux SEP: parkinsonisme, akathisie, dystonie, dyskinésie bucco-linguale, dyskinésie tronc-membre et dyskinésie totale.

3.2.2 Evaluation neuropsychologique

3.2.2.1 Fonctions exécutives

Le test d'assortiment de cartes du WCST est couramment utilisé en neuropsychologie pour évaluer les fonctions exécutives (Lezak, 1995). Le nombre de catégories détectées et les différents types de persévération sont les deux variables les plus fréquemment évaluées dans les études sur la SZ. Cette tâche consiste à placer des cartes dans la bonne catégorie selon les critères associés à la couleur, la forme ou

le nombre. Le participant doit apparier chacune des cartes dans la bonne catégorie selon une règle qui ne lui est pas indiquée. Il doit donc découvrir cette règle à partir des rétroactions de l'expérimentateur (correcte ou incorrecte).

3.2.2.2 Attention

Le d2 est une tâche de discrimination visuelle couramment utilisée pour évaluer les troubles d'attention sélective (Lezak, 1995). Le participant doit barrer le plus grand nombre de cibles (la lettre « d ») tout en ignorant les autres distracteurs similaires à la lettre cible. Le temps d'exécution du participant est noté pour chaque ligne.

3.2.2.3 Mémoire verbale

La capacité d'apprentissage et de rétention d'un matériel verbal a été évaluée à l'aide du California Verbal Learning Test (CVLT; Delis et al., 1987). Ce test est constitué de deux listes, A et B, présentées au sujet comme étant des listes d'achats pour le lundi et le mardi. La première liste (liste A) est composée de 16 mots répartis en 4 catégories sémantiques (légumes, meubles, moyens de transport, animaux). La liste A est présentée 5 fois consécutives et après chaque présentation un rappel libre est demandé au participant. Ensuite, la liste B est présentée pour un seul essai dans le but de créer de l'interférence. Cette seconde liste contient 2 catégories sémantiques tirées de la liste A et 2 nouvelles catégories (instruments de musique, fruits). Immédiatement après la présentation de la liste B, un rappel libre et un rappel indicé de la liste A est demandé au participant. Suite à un délai de 20 minutes, un rappel libre et un rappel indicé de la liste A sont demandés au participant. Enfin, une liste de 44 mots est lue à voix haute par l'expérimentateur. Cette liste est composée de mots des listes A et B, ainsi que des mots sémantiquement et phonologiquement

semblables à la liste A. Le participant doit indiquer si les mots faisaient partie de la liste A.

3.2.2.4 Apprentissage procédural

L'apprentissage procédural a été évalué à l'aide du computer-controlled Procedural Learning Tester (PLT; Cohen, 1997). Cette tâche de lecture en miroir permet de mesurer la capacité à acquérir une nouvelle compétence ainsi que l'automaticité de cet apprentissage. Le PLT se divise en 2 sous-tests. Le premier comporte 8 pairs de mots dont la disposition des lettres est orientée normalement et permet d'évaluer la capacité à lire du participant. Le second sous-test constitue la tâche procédurale de lecture en miroir. Les mots, composés de lettres inversées à la verticale, sont présentés par paires et selon une hiérarchie de complexité sémantique. Les catégories sont les suivantes : (C1) association sémantique typique, (C2) association non-sémantique typique, (C3) association sémantique atypique et (C4) association non-sémantique atypique. Ce sous-test contient au total 4 blocs de 24 paires de mots. La répartition des catégories sémantiques est équivalente pour l'ensemble des 4 blocs. Le temps de réaction est noté pour chacun des sous-tests.

3.3 Analyses statistiques

Une transformation des données (logarithme) a été effectuée à chaque fois que la distribution non homogène (asymétrie) des groupes a été rencontrée. Des ANOVAs à mesures répétées ont été menées sur les scores de performance aux différents tests neuropsychologiques (WCST, d2, CVLT, PLT) pour déterminer dans quel mesure les NLPs ont un effet sur les compétences cognitives des schizophrènes, comparé à la performance du groupe contrôle. Un effet principal de groupe (NLP typique, NLP atypique, contrôle) devait être observé pour ensuite effectuer des analyses *a posteriori* et préciser lequel des groupes diffère des autres groupes. Un

effet principal de temps (0, 3, 6, 12 mois) devait être observé afin de mener des analyses *a posteriori* et déterminer à partir de quel moment l'effet s'est manifesté. Enfin, une interaction groupe par temps devait être observée afin de conclure à une efficacité supérieure d'un NLP sur le fonctionnement cognitif.

Des analyses de corrélation de Pearson ont été effectuées sur les scores de performance aux tests neuropsychologiques et les scores du PANSS afin de déterminer les relations entre les performances cognitives et la sévérité des symptômes psychopathologiques associés à la schizophrénie.

CHAPITRE IV

ARTICLES PUBLIÉS

PREMIER ARTICLE

Rémillard, S., Pourcher, E., & Cohen, H. (2005). The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: A one-year follow up study. *Schizophrenia Research, 80,* 99-106.

Le but de cette étude était de déterminer l'effet différentiel de la rispéridone et de l'halopéridol sur les fonctions exécutives de personnes schizophrènes sur une période de 12 mois. Le WCST a été administré à 0, 3, 6 et 12 mois auprès de 31 participants schizophrènes répartis aléatoirement en deux groupes de traitements NLPs : 15 participants schizophrènes ont été traités avec la rispéridone et 16 avec l'halopéridol. La performance des deux groupes de participants schizophrènes a été comparée à celle d'un groupe contrôle constitué de participants sains. L'évaluation de la relation entre la performance au WCST et les symptômes positifs et négatifs de la schizophrénie a été considérée. Les résultats montrent que la performance des participants schizophrènes est déficitaire comparativement à celle du groupe contrôle, et ce, à chacune des périodes d'évaluation. De plus, la performance au WCST des participants traités avec rispéridone ne diffère pas de celle des participants traités avec halopéridol. Cependant, les participants sous rispéridone montrent une réduction significative des symptômes négatifs de la schizophrénie contrairement à ceux traités avec halopéridol. L'absence de relation entre la réduction des symptômes et les fonctions exécutives suggère que les manifestations psychopathologiques de la schizophrénie sont indépendantes des anomalies cérébrales qui sous-tendent les fonctions exécutives.

The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: A one-year follow up study

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4.1 Abstract

Cognitive dysfunctions (as in memory, attention and executive function) have been recognized as fundamental features of schizophrenia. Executive dysfunction is a major obstacle to functional outcome, community functioning and rehabilitation success and it is crucial to assess the effects of so-called neuroleptic (NLP) medications in this domain of cognitive functioning. Risperidone, an atypical NLP, has been reported to improve executive function in schizophrenia (SZ), but there is controversy regarding these findings. The aim of the current study was to assess the differential effects of risperidone (2-6 mg) and conventional (2-40 mg haloperidol) NLPs on executive skills in 31 individuals with SZ over a 12-month period. The performance of both NLP groups was compared to the performance of 17 age- and education-matched healthy controls. In this randomized, double blind study, the Wisconsin Card Sorting Test (WCST) was administered at baseline, 3, 6, and 12 months after initiating medication. The relationship between executive functioning and the course of clinical symptoms, as assessed by the Positive and Negative Syndrome Scale (PANSS) was also investigated. Results showed that, relative to

healthy controls, individuals with SZ showed marked impairment in WCST from baseline through 12 months of treatment. Also, participants under haloperidol or risperidone NLP medication performed similarly on the WCST at all assessment periods showing that risperidone and haloperidol do not differ in their effect on executive functioning. Risperidone treatment, however, was more effective in the reduction of negative symptoms. The differential efficacy of risperidone over negative symptoms and WCST performance strongly suggests that the executive impairments are to some extent the result of brain abnormalities independent of those that produce the major psychopathology manifestations seen in SZ.

Keywords: Risperidone; Haloperidol; Executive function; Symptomatology; Schizophrenia; Long-term treatment.

4.2 Introduction

Cerebral and functional impairments, particularly in the frontal lobes, have long been seen as an important component of a broad spectrum of dysfunctions in schizophrenia (SZ; Harvey et al., 1999; Ritter et al., 2004; Saykin et al., 1994). Among others, impairments in set shifting, mental sequencing, cognitive flexibility, and working memory have been associated with frontal dysfunction in SZ. Several of these impairments can be measured with the Wisconsin Card Sorting Test (WCST; Berg, 1948), a commonly used test to assess executive functioning in research with SZ (Heaton et al., 1993). More precisely, performance on the WCST has been correlated with brain activity in the dorsolateral prefrontal cortex (DLPFC) region in neuroimaging studies (Berman et al., 1995; Marenco et al., 1993). Also, Weinberger et al. (1986) showed that individuals with SZ show lower regional cerebral blood flow in the DLPFC during performance of the WCST, compared to healthy controls.

Cognitive function (and dysfunction) is predictive of work performance, social functioning and quality of life (Green, 1996; Meltzer and McGurk, 1999; Velligan et al., 1997). Executive function as assessed by WCST, is a good predictor of social and work outcomes (Addington and Addington, 2000; Green, 1996; Meltzer and McGurk, 1999). As neurocognitive dysfunctions may contribute to poor outcome and may constitute a considerable inconvenient to the rehabilitation of individuals with SZ in the community, an objective of drug treatment should be to enhance cognitive functioning (Kasper and Resinger, 2003).

Since the introduction of risperidone, an atypical NLP treatment, it has been observed that this drug can enhance cognitive function in SZ, a property that has not been associated with conventional NLP treatments (e.g., Meltzer and McGurk, 1999). However, there are important variations in the reported effects of risperidone NLP medication on the executive dysfunction observed in individuals with SZ. Some authors observed significant improvements in a wide range of neuropsychological tests, including WCST, with SZ patients receiving 2-6 mg/day of risperidone (Borkowska et al., 2002; Harvey et al., 2003; Rossi et al., 1997). In contrast to conventional NLP treatment (10-30 mg/day of haloperidol), Bilder et al. (2002) observed global neurocognitive improvement with olanzapine (10-40 mg) and risperidone (4-16 mg) over 3 months of treatment. In a longer duration study, comparing low dose of haloperidol (5 mg) with 6 mg of risperidone over 24 months, Green et al. (2002) found no significant difference between both NLP treatments on some neurocognitive tests (e.g. WCST, TMT B). Similarly, comparing treatments of 5-20 mg of haloperidol with 4-10 mg of risperidone over 12 months did not show significant differences between both NLP treatments on the performance of SZ patients, as measured by a wide range of neurocognitive tests including WCST (Purdon et al., 2000). In short, the limitations of some previous studies consist principally of methodological issues. Some studies were conducted on a short-term

basis (4-8 weeks), only one included healthy comparison group and others explored the effects of only one NLP or did not used conventional NLP as a comparator group.

Although the mechanism of possible cognitive enhancement with atypical NLP treatments (including risperidone) remains unclear, some hypotheses have been suggested. Namely, the effect can be a direct consequence of the drugs on dopamine activity in the prefrontal cortex (PFC; Cuesta et al., 2001; Friedman et al., 1999; Okubo et al., 1997), or can be related to the improvement of clinical symptoms, especially negative symptoms (Hong et al., 2002).

Given that the PFC dopamine plays an important role in cognition, the ability of most atypical NLPs, including risperidone, to improve executive function over typical NLPs may be associated to their distinct pharmacological profile. Greater $5HT_{2A}$ receptors blockade is a common characteristic of most atypical NLPs. In contrast to haloperidol, risperidone is characterized by a high $5HT_{2A}/D_2$ ratio. Thus, it as been found that the antagonism of serotonin $5HT_{2A}$ receptors activates dopaminergic neurons localized in the A10 nucleus (the ventral tegmental area) that projects to the PFC. The consequent release of dopamine in the PFC may thus have beneficial effects on the improvement of cognitive dysfunction (Friedman et al., 1999).

Risperidone was found to be as effective as haloperidol in reducing the positive symptoms of SZ, but also improved negative symptoms to a greater extent than conventional NLP medication (Bondolfi et al., 1998; Conley and Mahmoud, 2001, Peusken, 1995; Rabinowitz and Davidson, 2001; Yen et al., 2004). The effectiveness of risperidone to treat negative symptoms of SZ may be attributable to its greater affinity to serotonin $5HT_{2A}$ receptors than for D_2 receptors (Stip et al., 2005). Taking into account that the primary goal of NLP medication in SZ is to attenuate the

intensity of symptomatology, it has been suggested that the impact on cognition may arise from secondary effects. Consequently, several studies have been conducted in an attempt to determine whether there is a relationship between cognitive deficits and the severity of psychopathology in individuals with SZ. The relation between negative symptoms and executive dysfunction has been suggested by some who showed that increased negative symptomatology is associated with poor WCST performance (Basso et al., 1998; Berman et al., 1997; Heydebrand et al., 2004; Voruganti et al., 1997) and by others who noted that a reduction in positive symptoms was related to an improvement in various cognitive domains (Hoff et al., 1999; Ritter et al., 2004). Nevertheless, there is still controversy regarding the association between the improvement of psychopathology symptoms in SZ and cognitive functioning (Collins et al., 1997; Hughes et al., 2002).

In this perspective, the principal objective of this study was to examine the long-term effects of typical haloperidol and atypical risperidone NLPs on executive functioning in SZ patients, relative to the performance of a healthy control group. A further objective was to establish the long-term effects of haloperidol and risperidone NLP treatments on positive and negative symptoms in SZ.

4.3 Method

4.3.1 Participants

Thirty-one outpatients with a diagnosis of SZ (DSM-III criteria) participated in the study. One group of 15 patients (11 men, 4 women) was treated with risperidone and a second group of 16 patients (12 men, 4 women) received haloperidol. The mean age of the participants, age at onset of disease, duration of psychiatric illness and level of education were not statistically different between the two patient groups (all p's $>$ 0.05). A group of 17 healthy volunteers, matched for age and education, with no

history of psychiatric or neurological disorder and not currently under psychoactive medication also participated in the study. Exclusion criteria for all participants included a history of drug or alcohol abuse or neurological disease. Written informed consent was obtained from all participants. Demographic and clinical characteristics of the participants are presented in Table 1.

----------Insert Table 1 about here----------

4.4.2 Tests and Procedure

Participants were followed for 12 months and each participant completed the WCST (Berg, 1948) and the PANSS (Kay et al., 1989) at baseline, 3 , 6, and 12 months of treatment. The experimenter was blind to the identification and clinical information of the participants and the clinician assessing psychopathology was blind to the participant's cognitive performance. The WCST is a widely used test of executive functions, measuring cognitive flexibility and maintenance of a cognitive set. In this test, the participant is asked to determine the established sorting criterion (color, form, or number) through trial and error, and then shift to a new criterion according to a change in examiner feedback. The degree of psychopathology is assessed with the PANSS, a 30-item test. Each item is rated from 1 (no evidence) to 7 (extreme). A higher score is indicative of a more severe illness. At baseline, all SZ participants were on a stable regimen of haloperidol. SZ participants were then randomly assigned either on the same drug regimen or to a switching crossover design of substitution of haloperidol by risperidone. In the switching group, the baseline dose of conventional drug followed a 25% decrease each week until the dose reached 0 mg and a weekly progressive titration of risperidone of 0.5 mg BID, 1 mg BID, 1.5 mg BID, 2 mg BID with a further adjustment of 0.5 mg once or twice a day if judged clinically advantageous. Most of the participants reached final dosage at 4 weeks and all were stabilized within 8 weeks.

4.4.3 Data analyses

An alpha level of .05 was used for all statistical tests. Change in executive performance after treatment with typical or atypical NLP was analyzed using an analysis of variance (ANOVA) with repeated measures, with Group (risperidone, haloperidol, control) as between-subject factor and Time (baseline, 3, 6, 12 months) as within-subject factor. ANOVAs were conducted to determine whether differences existed between SZ patients receiving risperidone or haloperidol relative to healthy controls on each of the WCST measures (i.e., the number of categories completed and perseverative errors), throughout the assessment period. ANOVAs were performed on transformed (log10) data for perseverative errors scores. ANOVAs with Group (risperidone, haloperidol) and Time, with repeated measures on the second factor, were conducted to examine the differential effects of haloperidol and risperidone NLP treatment on positive and negative symptoms in SZ.

4.4 Results

4.4.1 Long-term effects of neuroleptic medication on executive functioning.

Main effects of Group were observed for WCST-Categories completed ($F(2,45)=14.98$, $p < 0.0001$, Effect Size (ES)= 0.40) and WCST-Perseveration ($F(2,45)=13.85$, $p < 0.0001$, ES=0.38). There was no significant Group by Time interaction. Post-hoc analyses were conducted to determine which group differed significantly from the others (schizophrenic vs. control; risperidone vs. haloperidol) in WCST performances. The results revealed that control participants performed better than the SZ participants in the number of categories completed ($F(2,45)=28.16$, $p < 0.0001$, ES= 0.39) as well as in the number of perseveration errors ($F(2,45)=24.04$, $p < 0.0001$, ES = 0.34). There was no significant difference between the SZ participants' performances under both NLP treatments for number of categories ($F(2,45)=0.82$, $p = 0.3694$, ES=0.01) and perseveration errors

($F(2,45)=3.28$, $p = 0.0770$, ES=0.05). The performance of each group on the WCST is presented in Figure 1.

----------Insert Figure 1 about here----------

4.4.2 Long-term effects of neuroleptic treatment on symptomatology.

The results of interest were a main effect of Time for PANSS negative symptoms ($F(3,87)=3.75$, $p < 0.0139$, ES=0.10) only, suggesting that all participants apparently improved on negative symptomatology over the duration of treatment. However, a Group by Time interaction for PANSS-negative symptoms ($F(3,87)=3.21$, $p < 0.0268$, ES=0.09) showed that there was a differential effect of treatment on the evolution of symptomatology. Post-hoc within-subject analyses for the risperidone group showed a significant difference between baseline and 3 to 12 months of treatment ($F(3,42)=13.50$, $p < 0.0007$, ES=0.06), indicating that risperidone is effective in the reduction of negative symptoms after 3 months. Further comparisons between 3 months and 6 to 12 months showed no difference in effect of treatment ($F(3,42)=1.39$, $p = 0.2456$, ES=0.01) nor between 6 months and 12 months ($F(3,42)=0.12$, $p = 0.7356$, ES= 0) suggesting that the early efficacy effect of risperidone in the reduction of negative symptoms remained constant for the duration of the study. Post-hoc within-subject analyses revealed no difference in evolution of negative symptomatology for the haloperidol group between baseline and 3 to 12 months ($F(3,45)= 0$, $p=0.9573$, ES= 0), 3months and 6 to 12 months ($F(3,45)= 0.55$, $p=0.4627$, ES= 0), nor between 6 months and 12 months ($F(3,45)=0.47$, $p=0.4979$, ES= 0). The course of the clinical symptomatology throughout the duration of the study for both treatment groups is illustrated in Figure 2.

----------Insert Figure 2 about here----------

4.4.3 Relationship between executive functioning and symptomatology.

Spearman *r* correlations were computed to examine the relation between measures of executive functioning and psychiatric symptoms in SZ, under the two treatment conditions. Each measure of the WCST (the number of categories completed and perseverative errors) was correlated with positive and with negative symptom scores of the PANSS. There was no relationship whatsoever between positive or negative symptoms and WCST performance in both treatment conditions.

4.5 Discussion

The aim of this study was to determine the differential long-term effects of typical haloperidol and atypical risperidone NLP treatments on executive functioning and the symptomatology of patients with SZ. The relationship between the severity of schizophrenic symptomatology and executive dysfunction was also examined. Our observations showed that the performance of SZ participants was significantly worse than that of healthy controls on all measures of the WCST, that there was no difference between the effects of risperidone and haloperidol on executive function, and that WCST performance remained essentially unchanged over the 12 months of the study. Our results also revealed a significant improvement in negative symptoms only with risperidone treatment, but not with haloperidol. Finally, the evolution of symptoms and executive function performance appear to follow independent courses, as there is no relationship between WCST measures and negative and positive symptoms in this group of SZ participants.

As revealed by neuroimaging studies, WCST involves DLPFC brain activity (Berman et al., 1995; Marenco et al., 1993; Weinberger et al., 1986). Given that the SZ participants' performances on the WCST did not improve under haloperidol or risperidone NLPs, this suggests that the pharmacological properties, which distinguish both NLPs, do not have the capacity to affect this specific cerebral area. That is, the hypothesis describing cognitive enhancement with atypical NLPs action

on $5HT_{2A}$ receptors in the PFC (Friedman et al., 1999), failed to explain why risperidone has so little effect on WCST performance in our study.

As measured by WCST, both risperidone and haloperidol treatments failed to improve executive skills over time. Relative to control participants, individuals with SZ exhibited significant impairment on the WCST. This deficit remained throughout the 12 months treatment. Our results do not agree with those of studies reporting a beneficial effect on WCST performance with SZ participants receiving risperidone medication (Bilder et al., 2002; Borkowska et al., 2002; Harvey et al., 2003; Rossi et al., 1997). In some of these studies, the length of the treatment period was as brief as 4 to 8 weeks (Harvey et al., 2003; Borkowska et al., 2002; Rossi et al., 1997). In addition to using a randomized double-blind design, the inclusion of healthy controls and a conventional antipsychotic comparator group may account for the divergence between our findings and those of previous studies. Our results, however, accord with a one-year study conducted by Purdon et al. (2000), which noted improvement of WCST performance with olanzapine, but not with risperidone or haloperidol. The findings of our study, which compared 11.7 mg of haloperidol with 4.5 mg of risperidone, are similar to those observed with lower dose of haloperidol (5 mg), as reported by the 24 months study conducted by Green et al. (2002).

Given that atypical NLPs are a heterogenous group of drugs with different pharmacological profiles, those results must not be generalized to all type of atypical NLPs (such as clozapine, olanzapine and quetiapine), but only to risperidone treatment in chronic SZ of previous conventional neuroleptization. Considering that chronic SZ patients are very little sensible to test for cognitive changes, it can be also interesting to explore neurocognitive profiles following long-term neuroleptization in a naïve sample. The significant contribution of our study, conducted over a one-year follow-up, in a randomized double-blind fashion and including a healthy control group, represents an important replication of findings in line with similar previous

long-term studies (Green et al., 2002; Purdon et al., 2000). Nevertheless, our findings must be interpreted with caution, as the results reported in this study focus on a single test (as a part of a wider range of neurocognitive assessments).

Treatment with risperidone showed significant reduction of negative symptoms in SZ at three months after initiation of treatment and this effect remained constant throughout the 12-month trial. Our results that risperidone has a higher efficacy than haloperidol in the reduction of negative symptoms is in accord with most previous studies (e.g., Bondolfi et al., 1998; Peuskens, 1995; Rabinowitz and Davidson, 2001; Yen et al., 2004). Risperidone possesses serotonergic and dopaminergic antagonist properties that may make it more effective than typical NLPs in the treatment of SZ negative symptoms (Carman et al., 1995). However, it is not clear if the superiority of risperidone in reducing negative symptoms is ascribed to its high $5HT_2$ affinity or to the discrepancy between striatal D_2 receptor occupancy of the NLPs used in our study (4.5 mg of risperidone and 11.7 mg of haloperidol). Positron emission tomography (PET) studies have shown that D_2 receptor occupancy in patients on stable doses of risperidone varies from an average of 66% on 2 mg/day to 79% on 6 mg/day (Kapur et al., 1995) while doses of haloperidol (10-20 mg/day) give more than 90% D_2 occupancy. It is also known that D_2 striatum occupancy greater than 80% is associated with increased incidence of EPS (Farde et al., 1992; Kapur et al., 2000). That is, extensive side effects associated with typical NLPs can cause or exacerbate certain negative symptoms, such as affective flattening and avolition (Heinz et al., 1998).

An objective of the present study was to identify the relationship between executive function and the course of the symptomatology in SZ. Neither positive nor negative symptomatology was associated with any of the WCST scores for the duration of the study, for both treatment groups. Others had reported an association between clinical symptoms and executive function (Basso et al., 1998; Berman et al., 1997;

Heydebrand et al., 2004; Voruganti et al., 1997), but this divergence with our results is not clear and probably reflects the effect of previously described methodological constraints. Nevertheless, the differential efficacy of risperidone over negative symptoms and WCST performance strongly suggests that the executive impairments are to some extent the result of brain abnormalities independent of those that produce the major psychopathology manifestations seen in SZ.

The course of cognitive change in patients with SZ following atypical medication can only be determined with longer-term studies (Harvey and Keefe, 2001). The main contribution of the present study was an effort to determine the long-term effects of typical haloperidol and atypical risperidone medication on SZ clinical symptoms and on executive function relative to the performance of a healthy control group.

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4.5.1 Table 1 : Clinical and demographic characteristics

	Risperidone *n* = 15	Haloperidol *n* = 16	Control *n* = 17	Statistical results
Sexe (men: women)	11: 4	12: 4	9: 8	
Mean age, yr (SD)	41.9 (9.5)	46 (9.9)	41.6 (9.7)	P > 0.05
Mean education, yr (SD)	11.5 (3.6)	11.4 (2.9)	13.3 (2.6)	P > 0.05
Mean age of onset, yr (SD)	26.3 (6.8)	27.6 (9.2)		P > 0.05
Mean duration of disease, yr (SD)	15.5 (10.8)	18.4 (11.7)		P > 0.05
Mean dosage, *mg/day*, (SD)	4.1 (1.15)	11.7 (9.27)		
Range of NLP doses	(2-6 mg/day)	(2-40 mg/day)		

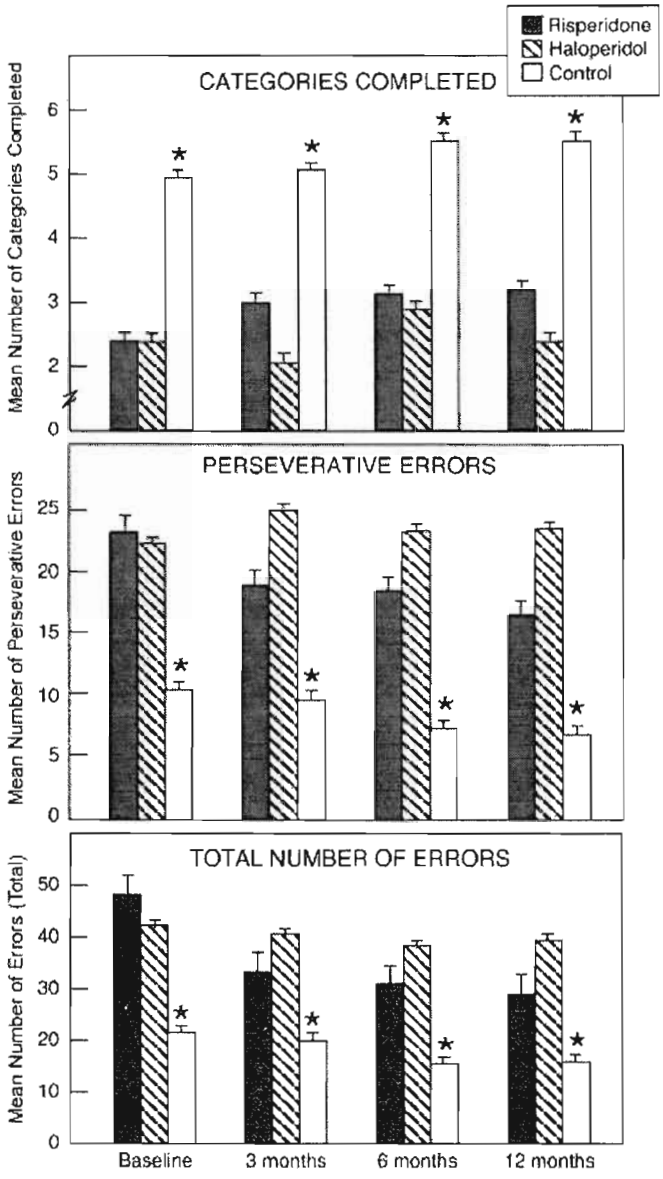
Figure captions

Figure 1. Mean performance scores on WCST over time for risperidone, haloperidol, and control participants.

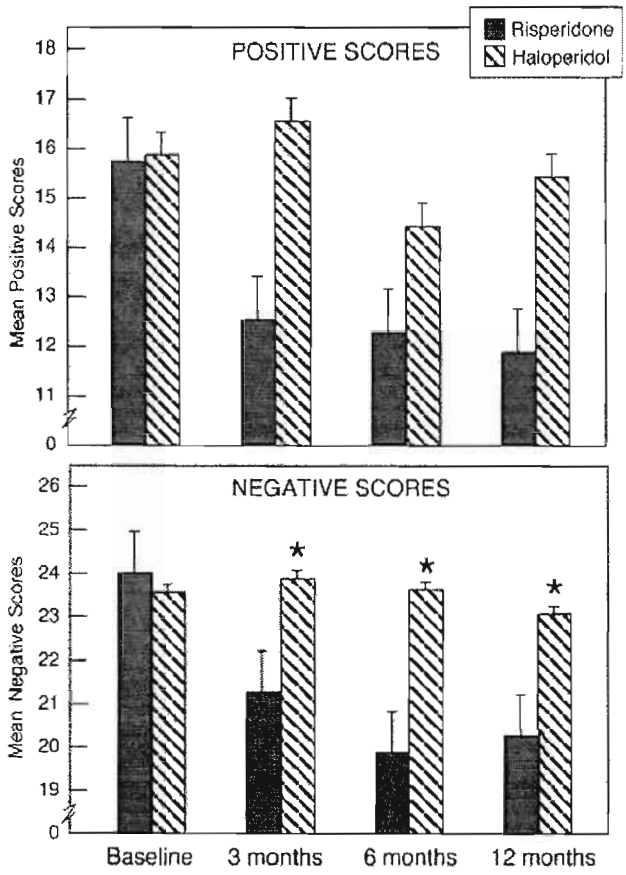
*: < .05

Figure 2. Mean scores on PANSS over time for risperidone and haloperidol treatment groups.

*: < .05



4.5.2 Figure 1. Mean performance scores on WCST over time for risperidone, haloperidol, and control participants.



4.5.3 Figure 2. Mean scores on PANSS over time for risperidone and haloperidol treatment groups.

DEUXIÈME ARTICLE

Rémillard, S., Pourcher, E., Cohen, H. (2008). The long-term effects of risperidone versus haloperidol on verbal memory, attention and symptomatology in schizophrenia. *Journal of the International Neuropsychological Society, 14,* 110-118.

L'objectif de cette étude était d'évaluer l'effet différentiel de l'halopéridol et de la rispéridone sur la mémoire verbale, l'attention et les symptômes psychiatriques de la schizophrénie. La performance de 28 participants schizophrènes, assignés aléatoirement à un groupe de traitement sous rispéridone (2-6 mg/jour) ou à un groupe de traitement sous halopéridol (2-40 mg/jour), est comparée à celle d'un groupe contrôle composé de participants sains. Le California Verbal Learning Test, le test d'attention d2 et le Positive and Negative Symptoms Scale ont été administrés à 0, 3, 6 et 12 mois. Comparativement au groupe contrôle, les schizophrènes montrent un déficit sur le plan de la mémoire verbale ainsi qu'un ralentissement significatif de la vitesse de traitement de l'information. Les deux groupes de NLPs montrent une performance similaire au CVLT et au d2 sur un suivi de 12 mois. Cependant, la rispéridone s'est avérée plus efficace que l'halopéridol pour diminuer les symptômes psychiatriques de la schizophrénie. Néanmoins, l'amélioration de la symptomatologie n'est pas associée à la performance cognitive. Ces résultats suggèrent que l'amélioration de la psychopathologie avec la rispéridone est indépendante des effets sur la cognition.

The long-term effects of risperidone vs. haloperidol on verbal memory, attention and symptomatology in schizophrenia

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Word Count: Abstract 191 words, Text 4 159 words

4.6 Abstract

There is evidence in the literature that cognitive functions in schizophrenia (SC) may be improved by atypical neuroleptics (NLPs) in contrast to typical medication, but there is still controversy regarding this apparent superiority of atypical drugs. In this study, we assessed the differential effects of risperidone and haloperidol on verbal memory, attention, and psychiatric symptoms in SC. The performance of 28 SC participants, randomly assigned to risperidone (2–6 mg/day) or haloperidol (2–40 mg/day), was compared to that of healthy controls. The California Verbal Learning Test (CVLT), the d2 Cancellation Test, and the Positive and Negative Symptoms Scale were administered at baseline and 3, 6, and 12 months. Relative to controls, all SC participants showed markedly impaired verbal memory and processing speed at each assessment period. There was no differential effect between the two NLPs on CVLT and d2 performance. However, risperidone was more effective than haloperidol in reducing psychiatric symptoms. Improvement in symptom severity was not associated with improvement in neurocognitive performance on these specific tests. Neither conventional nor atypical neuroleptic medications improved neurocognitive functioning over a 12-month follow-up, suggesting that psychopathological improvement under risperidone is independent of cognitive function.

Key Words: Cognitive impairment; Neuroleptic; Longitudinal assessment; Neuropsychological deficits; Speed processing; Recall.

4.7 Introduction

Neurocognitive impairments of verbal learning and memory are among the most severe symptoms of schizophrenia (SC; Aleman et al., 1999; Hill et al., 2004; Paulsen et al., 1995) and have a major impact on patients' everyday activities (Green, 1996). Structural and functional neuroimaging studies in SC have shown evidence of a dysfunction affecting the hippocampus, a brain region that underlies specific memory and learning functions such as conscious recollection of deeply encoded items (Fukuzako et al., 1995; Heckers et al., 1998; Weiss et al., 2004). The hippocampus plays a determining role in the consolidation of short-term memory stores in long-term memory. Dysfunction of the left frontal cortex has also been associated with memory encoding deficits (Fletcher et al., 1998; Shallice et al., 1994; Tulving et al., 1994). Specifically, performance on verbal learning tasks, such as the California Verbal Learning Test (CVLT; Delis et al., 1987) has been associated with brain activity in both the hippocampus and the prefrontal cortex of healthy participants (Johnson et al., 2001). Since attention processes have been associated with activity in the prefrontal brain area (Toichi et al., 2004; Vendrell et al., 1995), questions remain as to whether memory impairments may be caused by other cognitive difficulties such as attentional dysfunction. Thus, some authors have suggested that problems with sustained and focused attention underlie the poor memory performance of patients with SC (Holthausen et al., 2003; Nuechterlein & Dawson, 1984).

Since the introduction of risperidone, an atypical neuroleptic (NLP) treatment, there has been evidence of higher cognitive efficiency in SC patients treated with this NLP (Harvey et al., 2003). In contrast to typical drugs, neurocognitive improvements have been observed with risperidone treatment in the domain of verbal memory (Bilder et al., 2002; Kern et al., 1999) and attention (Harvey et al., 2000; Stip & Lussier, 1996). However, this is not always the case, as other studies have shown no difference between the effects of typical NLP and risperidone treatments on attention (Liu et al.,

2000) and verbal learning and memory (Cuesta et al., 2001; Green et al., 2002; Purdon et al., 2000; Stip & Lussier, 1996). These divergent results may be due to differing methodological approaches. In the majority of studies, there is no healthy comparison group (Bilder et al., 2002; Cuesta et al., 2001; Green et al., 2002; Harvey et al., 2003; Kern et al., 1999; Liu et al., 2000; Purdon et al., 2000; Stip & Lussier, 1996); other studies are conducted at a specific point in time (or over a rather short period; Bilder et al., 2002; Harvey et al., 2000; Harvey et al., 2003; Hong et al., 2002; Kern et al., 1999; Liu et al., 2000); and some considered the effects of a single treatment only (Stip & Lussier, 1996) or did not use a conventional NLP as a comparison group (Harvey et al., 2003).

Different hypotheses regarding the cognitive enhancement seen with atypical NLP treatment have been proposed. Selectivity for dopaminergic modulation in the mesolimbic and prefrontal cortex, avoiding the D_2 blockade in the associative and sensorimotor parts of the basal ganglia, is one suggestion; this would result in a reduced need for anticholinergic medication and a direct benefit on verbal memory abilities (Kern et al., 1999). Mori et al. (2002) observed a significant improvement in the immediate memory and verbal working memory of SC patients after anticholinergic treatment had been withdrawn for two weeks. Other authors have also reported that higher anticholinergic drug dosages are associated with deficits in free recall (Paulsen et al., 1995) and reduced semantic clustering (Strauss et al., 1990). Another explanation derives from the mixed $5HT_2/D_2$ receptor blockade property common to atypical NLPs, which has been shown experimentally to increase the release of dopamine in the prefrontal cortex, with a direct impact on attention and working memory (Meltzer & McGurk, 1999). A third explanation of verbal memory enhancement with atypical NLPs is directly linked to optimal control over clinical symptoms, especially negative symptoms (Hong et al., 2002). Atypical drugs have been found to improve psychopathological symptoms over conventional NLP drugs. Risperidone was found to be more effective than haloperidol in reducing the positive

symptoms of SC, but also improved negative symptoms of individuals more than conventional NLP medications (Peuskens, 1995; Rabinowitz & Davidson, 2001; Yen et al., 2004). Thus, the aim of many studies was to investigate the relationship between neurocognitive dysfunction and the severity of psychopathology in individuals with SC. Bozikas et al. (2004) found the severity of negative symptoms to be mainly correlated with deficits of executive functions, semantic memory, and verbal memory. Aleman et al. (1999) also observed an association between poor memory performance and negative symptoms in SC patients. However, there is still some controversy regarding the association between improvements in cognitive symptoms and in psychiatric symptoms, as a number of studies have failed to reveal any relationship between either negative or positive symptoms and cognitive performance, including attention and verbal memory (Epstein et al., 1996; Hughes et al., 2003; Liu et al., 2000; Rémillard et al., 2005).

4.8 Aims of the study

From this perspective, the aim of the present study was to determine the long-term effects of two classes of NLPs, typical haloperidol and atypical risperidone, on attention and verbal memory functions in chronic schizophrenic patients, relative to the performance of a healthy control group. Further objectives were to determine the extent to which aspects of the clinical status of patients (psychiatric symptoms, parkinsonian extrapyramidal symptoms, anticholinergic medication) are associated with differences in neurocognitive performance.

4.9 Material and methods

4.9.1 Participants

Twenty-eight outpatients with a diagnosis of SC were recruited for this study. The diagnosis of SC was made in accordance with the DSM-III-R criteria, for all patients and by the same psychiatrist. Fourteen patients (11 men, 3 women) were selected at

random to switch from a stable treatment with haloperidol to risperidone over a month, while 14 patients (11 men, 3 women) were selected at random to maintain haloperidol at their previous dosages. The mean age of the participants, age at diagnosis, duration of psychiatric illness or treatment, and level of education were not statistically different between the two patient groups (all p's > .05). A group of 18 healthy volunteers, with no history of psychiatric or neurological disorders and not currently taking psychoactive medication, was included in the study. This control group was matched with the two patient groups for age and education. None of the participants in the study had a history of drug or alcohol abuse or neurological disease and none required hospitalization for the duration of the study. Table 1 shows the demographic and clinical characteristics of each group. Written informed consent was obtained from each participant. The study was carried out according to the principles laid down in the Helsinki declaration and it was approved by the Centre de recherche Université Laval-Robert-Giffard ethics committee.

----------Insert Table 1 about here----------

4.9.2 Tests and procedure

The study design included four assessment periods: at baseline, 3, 6, and 12 months. The first assessment was conducted at baseline, when all the 28 SC participants were on a stable regimen of haloperidol. After the first assessment, they were then randomly assigned either to the same drug regimen or to a switching crossover design involving substitution of haloperidol by risperidone. In the switching group, the baseline dose of the conventional drug decreased by 25% each week until the dose reached 0 mg, while there was a weekly progressive titration of risperidone of 0.5 mg BID, 1 mg BID, 1.5 mg BID, and 2 mg BID with a further adjustment of 0.5 mg once or twice a day if judged clinically advantageous. Most of the participants reached the final dosage at 4 weeks and all were stabilized within 8 weeks. A steady state of neuroleptization was maintained over one year and lorazepam was allowed on an as-

needed basis except during the week before each test. During the course of the study, patients were administered anticholinergic medication (Procyclidine or Benztropine) as needed. The same psychiatrist consultant administered all the patients' medications.

At each assessment session, all participants were administered an adaptation of the California Verbal Learning Test (CVLT; Delis et al., 1987) in Canadian French (Nolin, 1999) and the d2 Cancellation Test of attention (Brickenkamp & Zillmer, 1998). The French version of the CVLT was administered in two different forms in order to avoid practice effects and the order of administration of these forms was permuted across assessment periods (Form 1 at 0 month, Form 2 at 3 months, then Form 1 again at 6 months, and Form 2 at 12 months). These two forms of the CVLT have been validated in Canadian French (Nolin, 1999) and, as with the original English version, the test consists of two shopping lists of 16 items (with 4 items from each of 4 categories). The CVLT is a test of verbal memory and learning, which provides information on immediate recall, delayed recall and learning strategies such as semantic organizational strategy. The following CVLT variables were selected for analysis: total recall (the sum of trials 1 to 5), semantic cluster ratio score, short-delay free recall (immediately after the interference task), and long-delay free recall (approximately 20–30 minutes after initial learning). The d2 Cancellation Test requires participants to cross out the letter *d* surrounded by two dashes while ignoring distractor letters and dashes. This test measures selective and sustained visual attention, psychomotor processing speed and response inhibition. The mean number of errors and the mean value of response times were used as scores.

Changes in symptom severity were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989), a 30-item test. The score for each item ranges from 1 (no evidence) to 7 (extreme). The Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al., 1980) was used to assess the severity of

extrapyramidal symptoms (EPS). Parkinsonian symptoms can impact on the performance of cognitive tasks with a psychomotor component. The score for parkinsonian symptom ratings was therefore used for subsequent analyses. For the duration of the study, the experimenter was blind to the participants' medication and psychopathological status, while the clinician assessing psychopathology and EPS was blind to their cognitive performance and medication status.

4.9.3 Data analyses

An alpha level of 0.05 was used for all statistical tests. The changes in cognitive performance measures (verbal memory and attention) after treatment with typical or atypical NLPs were analyzed using repeated-measures ANOVAs, performed separately for each variable, with Group (risperidone, haloperidol, control) as the between-subjects factor and Time (baseline, 3, 6, 12 months) as the within-subjects factor. Analyses were conducted to determine whether SC participants receiving risperidone or haloperidol differed from healthy controls on each of the CVLT and d2 measures over the 12-month follow-up. ANOVAs were performed on transformed (log10) data for semantic clusters and number of errors. In order to examine the differential effects of haloperidol and risperidone treatment on positive and negative symptoms in SC, ANOVAs with Group (risperidone, haloperidol) and Time, with repeated measures on the second factor, were performed on the PANSS positive and negative scores. When the sphericity assumption was violated, the Greenhouse-Geisser correction was used accordingly.

Additionally, post hoc within-subjects contrasts were performed on every significant main effect of Time, in order to determine when an improvement occurred over the duration of the study (baseline, 3, 6, 12 months). Moreover, post hoc between-subjects effects were also conducted each time a main effect of Group was observed, in order to determine which group differed from the other (SC vs. control; risperidone vs. haloperidol). To investigate the possibility that improved cognitive function

might be associated with clinical symptoms (PANSS, ESRS) or concomitant medication (anticholinergic drugs), post hoc analyses were performed computing Pearson correlation coefficients. The Statistical Package for Social Sciences 11 (SPSS) software was used for all statistical analyses.

4.10 Results

4.10.1 Cognitive and clinical changes

There were significant main effects of Group for CVLT recall trials 1 to 5 ($F(2,43)=18.63$, $p<.0001$, Eta-Squared (η^2)=0.46), semantic clustering ($F(2,43)=6.53$, $p<.003$, $\eta^2=0.23$), short-delay free recall ($F(2,43)=15,41$, $p<.0001$, $\eta^2=0.42$), and long-delay free recall ($F(2,43)=14.43$, $p<.0001$, $\eta^2=0.40$). Main effects of Time were also observed for CVLT recall trials 1 to 5 ($F(3,129)=12.73$, $p<.0001$, $\eta^2=0.23$), semantic clustering ($F(3,129)=4.5$, $p<.008$, $\eta^2=0.10$), short-delay free recall ($F(3,129)=13.51$, $p<.0001$, $\eta^2=0.24$), and long-delay free recall ($F(3,129)=6.94$, $p<.0001$, $\eta^2=0.14$). There was a significant Group by Time interaction for CVLT long-delay free recall ($F(6,129)=2.40$, $p=.03$, $\eta^2=0.10$) only. Non-significant Group by Time effects were observed for recall trials 1 to 5 ($F(6, 129)=1.74$, $p=.141$, $\eta^2=0.08$), semantic clustering ($F(6,129)=0.536$, $p=.747$, $\eta^2=0.02$), and short-delay free recall ($F(6, 129)=1.73$, $p=.119$, $\eta^2=0.08$).

Post hoc analyses were performed in order to determine which group, if any, differed from the others (SC vs. control; risperidone vs. haloperidol) in terms of CVLT performance. The results revealed that control participants performed better than both SC groups on recall trials 1 to 5 ($F(2,43)=37.21$, $p<.0001$, $\eta^2=0.46$), semantic clustering ($F(2,43)=13.03$, $p=.001$, $\eta^2=0.23$), short-delay free recall ($F(2,43)=30.74$, $p<.0001$, $\eta^2=0.42$), and in long-delay free recall ($F(2,43)=28.86$, $p<.0001$, $\eta^2=0.40$). There was no significant difference between the two groups of SC participants on all the CVLT measures (Trials 1 to 5 ($F(2,43)=0.006$, $p=.935$, $\eta^2 =0.00$); semantic

clustering ($F(2,43)=0.04$, $p=.859$, $\eta^2=0.00$); short-delay recall ($F(2,43)=0.04$, $p=.833$, $\eta^2.=0.00$); Long-delay recall ($F(2,43)=0.02$, $p=.896$, $\eta^2=0.00$)). Post hoc analyses were also performed to determine whether the main effects of Time were associated with a practice effect over the repeated assessments of the CVLT. The results revealed significant linear contrasts in three CVLT variables (recall trials 1 to 5, semantic clustering, short-delay free recall), suggesting a practice effect of the neurocognitive test for all participants over the assessment periods.

Further post hoc analyses on verbal long-delay free recall revealed an improvement over time under atypical risperidone treatment. Risperidone was effective at the 3-month ($F(1,13)=5.72$, $p=.033$, $\eta^2=0.31$) and 6-month assessments ($F(1,13)=7.36$, $p=.018$, $\eta^2=0.36$); performance remained stable thereafter until the 12-month assessment period ($F(1,13)=0.20$, $p=.66$, $\eta^2=0.02$). Post hoc tests for the haloperidol group also revealed a significant enhancement in long-delay free recall at 3 months ($F(1,13)=6.91$, $p=.02$, $\eta^2=0.35$). Improvement was also noted when participants were tested at 12 months ($F(1,13)=5.15$, $p=.04$, $\eta^2=0.28$). Post hoc analyses for the control group revealed no significant difference in long-delay free recall performance from baseline to 12 months. These results suggest either that both NLP treatments had a direct effect in improving long-delay recall performance or that there was a practice effect not seen in the healthy controls because their performance plateaued over the 12-month follow-up study. The performance of each group on the CVLT subtests is presented in Figure 1.

----------Insert Figure 1 about here----------

ANOVAs on selective attention performance showed a main effect of Group for response time scores ($F(2,43)=8.41$, $p<.001$, $\eta^2=0.28$) only. There was no effect of Group for number of errors ($F(2,43)=0.67$, $p=.517$, $\eta^2=0.03$). A main effect of Time was revealed for both measures of the d2 Cancellation Test, number of errors

($F(3,129)=4.49$, $p<.008$, $\eta^2=0.09$) and response time scores ($F(3,129)=13.88$, $p<.0001$, $\eta^2=0.24$). There was no interaction effect for both number of errors ($F(6,129)=0.91$, $p=.48$, $\eta^2=0.04$) and response time ($F(6, 129)=1.26$, $p=.29$, $\eta^2=0.06$).

Post hoc analyses were performed in order to determine which group differed from the others on processing speed performance. The results showed that control participants performed better than both NLP treatment groups ($F(2, 43)=15.72$, $p<.0001$, $\eta^2=0.27$). There was no significant difference between both haloperidol and risperidone groups in processing speed measures ($F(2,43)=2.1$, $p=.299$, $\eta^2=0.05$). Post hoc tests showed significant linear contrasts for response time variable. These results suggest a practice effect for all participants over the repeated administration of the d2 test. Further post hoc tests were conducted on the main effect of Time for number of errors. Results revealed significant linear contrasts suggesting a practice effect for all participants over the repeated assessments study. The performance of each group on the d2 test is presented in Figure 2.

----------Insert Figure 2 about here----------

There was a main effect of Group for both PANSS-positive ($F(1,26)=6.26$, $p=.019$, $\eta^2=0.19$) and PANSS-negative symptoms ($F(1,26)=5.61$, $p=.026$, $\eta^2=0.18$). The results of most interest were a Group by Time interaction for PANSS-negative symptoms ($F(3,78)=3.64$, $p=.04$, $\eta^2=0.12$), indicating a differential effect of NLP class treatment on the evolution of symptomatology. Post hoc analyses for the risperidone group showed a significant difference between the results at baseline and after 3 to 12 months of treatment ($F(1,13)=6.12$, $p=.028$, $\eta^2=0.32$) for the PANSS-negative, showing that risperidone is effective in reducing negative symptoms after 3 months. Further analyses showed no difference between assessment at 3 months and the other assessment periods (Level 2 vs. latter ($F(1,13)=0.67$, $p=.43$, $\eta^2=0.05$); Level

3 vs. level 4 ($F(1,13)= 3.86$, $p=.07$, $\eta^2 =0.23$)), suggesting that the early efficacy of risperidone in reducing negative symptoms remained stable until the end of the study.

For the haloperidol group, post hoc analyses revealed no difference in the evolution of negative symptomatology from baseline to the end of the follow-up study (Level 1 vs. later ($F(1,13)=0.49$, $p=.49$, $\eta^2 = 0.04$); Level 2 vs. later ($F(1,13)=0.025$, $p=.88$, $\eta^2 =0.002$; Level 3 vs. level 4 ($F(1,13)=0.408$, $p=.53$, $\eta^2 =0.03$)). Thus, there were no significant changes in symptomatology under typical NLP treatment. The course of the clinical symptomatology throughout the duration of the study, for both treatment groups, is presented in Figure 3.

----------Insert Figure 3 about here----------

4.10.2 Relationship between cognitive function, clinical status, and anticholinergic medication

Pearson correlations were conducted between CVLT scores, d2 scores, PANSS scores, ratings of parkinsonism, and anticholinergic medication. There was no steady relationship between cognitive performance and any of the clinical status and anticholinergic medication over all the one-year follow-up study. All values of the Pearson correlation coefficients are presented in Table 2.

----------Insert Table 2 about here----------

4.11 Discussion

The first objective of this study was to determine whether typical haloperidol and atypical risperidone treatments had a differential effect on SC subjects' verbal memory, attention, and symptomatology. The relationship between the severity of the

symptomatology and anticholinergic drugs, parkinsonian symptoms, and cognitive functioning was also examined.

Our results revealed that SC patients showed significantly poorer performance on verbal memory tests and attentional processing speed than healthy controls. In addition, risperidone and haloperidol treatments did not have a differential effect on verbal memory and processing speed throughout the study. With the exception of long-delay recall, the SC patients' cognitive performance remained essentially unchanged at all assessment periods relative to that of the healthy controls. Our observations also showed a significant reduction in negative symptoms under risperidone treatment but not with haloperidol. It appears that the evolution of symptoms, verbal memory performance, and processing speed performance all follow independent courses. Finally, anticholinergic drugs and parkinsonian EPS were not associated with memory or attention performance in these groups of SC patients.

Relative to healthy controls, participants with SC showed markedly impaired performance on the CVLT over the 12 months of the study. Our observations are in agreement with a number of studies reporting verbal learning and memory deficits in SC (Aleman et al., 1999; Hill et al., 2004; Paulsen et al., 1995). Most of these studies found that the verbal memory impairment seen in SC resulted from an encoding deficit, probably caused by the use of ineffective learning strategies. In our study, we observed that patients with SC recalled fewer items on the CVLT and used reduced semantic clustering strategies to hold information in memory. To some extent, our participants' use of poor semantic clustering may explain their inability to recall new information, such as a list of words, in an organized manner. It is noteworthy that impaired categorization and poor semantic clustering have also been observed in Parkinson's disease; parkinsonian patients were tested on the CVLT in two pharmacological conditions: the ON treatment (on levo-dopa therapy) and the practically OFF treatment (no levo-dopa intake after an overnight without treatment).

Poor semantic clustering was observed only in the OFF condition (Pourcher et al., 2000). Thus, encoding strategies may partly depend on an optimal prefrontal dopaminergic input.

Interestingly, verbal long-delay free recall was somewhat improved under both risperidone and haloperidol treatment—but the SC patients remained impaired relative to the control group. The improvement observed under risperidone treatment is consistent with some prior reports (Bilder et al., 2002; Harvey et al., 2003; Kern et al., 1999). However, the improvement with haloperidol is somewhat unexpected, as the majority of those studies had reported no cognitive enhancement with conventional treatment. In some of those studies, the duration of the treatment assessment was as short as 6 to 8 weeks (Harvey et al., 2003; Kern et al., 1999). In addition, the inclusion of healthy controls may account for the divergence between our findings and those of some previous studies. Our observations do, however, agree with a one-year study conducted by Lee et al. (1999), who found some improvement in delayed recall memory with typical NLPs, as measured by the Verbal List Learning Test (Buschke & Fuld, 1974). Nevertheless, even though different CVLT versions were used alternately to avoid a practice effect, our findings must be interpreted with caution. Since the control group's performance plateaued, the improvement under both NLP treatments may simply represent a practice effect due to the repeated administration of the CVLT. Treatment with risperidone or haloperidol failed to improve any of the other CVLT measures. These results are consistent with other studies showing similar observations (Cuesta et al., 2001; Green et al., 2002; Purdon et al., 2000; Stip & Lussier, 1996) and with a previous study (Rémillard et al., 2005) that reported similar effects on executive function.

The verbal memory impairment observed here is not explained by the use of anticholinergic medications, as there was no significant relationship between the anticholinergic drug dosages and any of the CVLT measures over the 12-month

assessment period. These findings are at odds with some previous research (Frith, 1984; Mori et al., 2002) reporting that anticholinergic drugs have a deleterious effect on verbal memory in SC. The cause of this divergence is not clear but a number of reports have also documented an absence of anticholinergic effect on verbal memory performance in SC (e.g., Green et al., 2002). It is very probable that anticholinergics have a different impact depending on the type, the dose and the population of schizophrenic patients studied.

With respect to attentional function, it was revealed that patients with SC do not produce more errors than control subjects on the d2 Cancellation Test. However, they take much more time to complete the task. These findings corroborate earlier reports of processing speed deficits in SC (Hong et al., 2002; Lussier & Stip, 2001). The processing speed deficit observed in this experiment, under both NLP medications, remained stable until the end of the 12-month follow-up.

Relative to healthy performance, neither NLP enhanced SC participants' processing speed on the d2 test. These results do not agree with previous studies reporting superior cognitive efficiency under risperidone treatment on some specific tests of attention (Harvey et al., 2000; Stip & Lussier, 1996). In those studies, the populations of patients were different: the disease duration and/or NLP exposure was shorter. However, the inclusion of a healthy control group and the long-term assessment of cognitive function suggest that these effects must be carefully evaluated with reference to so-called normal behavior over a sufficiently long period of time.
A significant reduction in both positive and negative psychiatric symptomatology was observed after initiating risperidone treatment. This is consistent with most previous studies, which found that psychiatric symptomatology improves more with risperidone than with typical NLP treatments (Peuskens, 1995; Rabinowitz & Davidson, 2001; Yen et al., 2004). Risperidone possesses serotonergic and

dopaminergic antagonist properties that may make it more effective than typical NLPs in the treatment of SC symptoms (Carman et al., 1995).

The majority of the CVLT measures, as well as processing speed, did not differ significantly in the risperidone and haloperidol groups over the course of the study, despite reduction in symptom severity under risperidone treatment. Moreover, there was no association between symptoms and cognitive impairment in either group of SC participants. Our results parallel studies that recognize cognitive dysfunction as a primary deficit that is independent of psychiatric manifestations and may persist after their resolution (Epstein et al., 1996; Hughes et al., 2003; Liu et al., 2000).

The complexity of psychiatric manifestations and cognitive function in SC and the pharmacodynamic properties of NLP treatments may benefit from longer-term studies. The contribution of the present study was an attempt to clarify the long-term effects of typical haloperidol and atypical risperidone medication on certain aspects of cognitive function in chronically ill and chronically treated patients relative to the performance of a healthy comparison group. These results do not, however, preclude the possibility that different benefits might be observed in a population of patients who were chronically treated from the onset of their disease and from a younger age with atypical NLPs, which have less impact on prefrontal functions. Only new long-term studies with a new generation of patients may provide clearer answers.

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4.11.1 Table 1: Demographic and clinical characteristics of participants

	Risperidone $n = 14$	Haloperidol $n = 14$	Control $n = 18$	Statistical results
Sex (men: women)	11:3	11:3	11:7	
Mean age, yr (SD)	40.6 (9.9)	44.1 (9.4)	41.2 (9.5)	$p > 0.05$
Mean education, yr (SD)	11.6 (3.8)	12.3 (2)	13.4 (2.6)	$p > 0.05$
Mean age at Diagnosis, yr (SD)	26.3 (6.2)	28.4 (9.8)		$p > 0.05$
Mean duration of continuous NLP treatment, yr (SD)	14.4 (10.6)	15.6 (10.2)		$p > 0.05$
Mean dosage, *mg/day* (SD)	4 (1.41)	13 (10.03)		
Range of NLP doses	2-6 mg/day	2-40 mg/day		
PANSS Positive (SD)	12.5 (4.2)	16 (4.9)		$*p < 0.05$
PANSS Negative (SD)	20.9 (4.9)	25.5 (6.01)		$*p < 0.05$
ESRS Parkinson (SD)	15 (8.6)	12.9 (9.5)		$p > 0.05$
Participants treated with anticholinergic medication, (n/14)	3	9		
- Mean dosage, *mg/day* (SD)	2.67 (1.15)	4.11 (2.47)		$*p < 0.05$
- Range of dosage	2-4 mg/day	1-8 mg/day		

T1= baseline, T2= 3 months, T3= 6 months, T4= 12 months

$*p < 0.05$

4.11.2 Table 2 : Correlation values between cognitive performance (CVLT and d2 test), clinical symptoms (PANSS, ESRS), and concomitant medication (anticholinergic drug) over time.

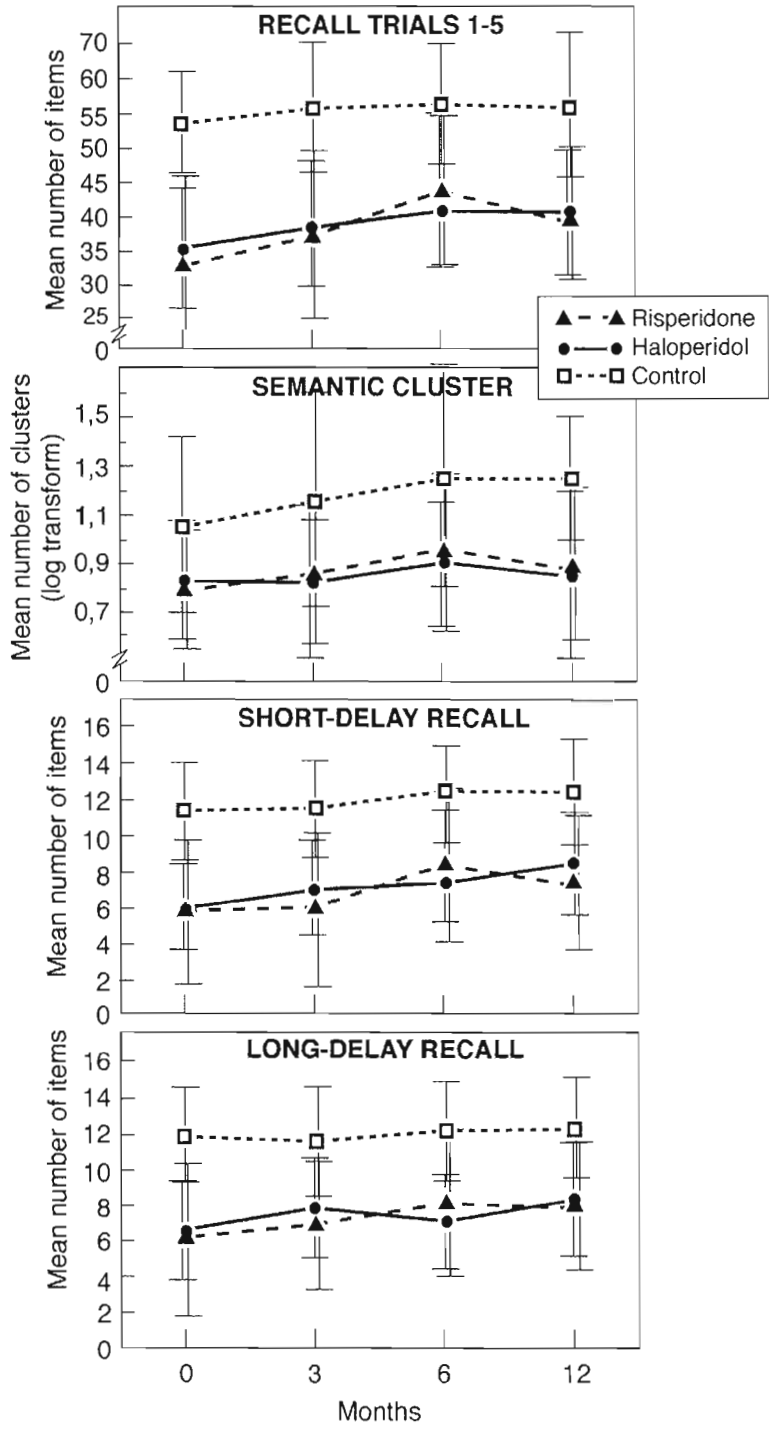
	CVLT (Sum of trials 1 to 5)				CVLT (Short-delay recall)				CVLT (Long-delay recall)			
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
PANSS POSITIVE	-.03	-.08	-.07	-.12	.09	.19	-.13	-.16	.06	.03	-.27	-.11
PANSS NEGATIVE	-.24	-.17	-.10	-.01	-.36	-.26	-.26	-.07	-.34	-.07	-.42*	-.06
ESRS PARKINSON	-.04	-.02	-.01	-.09	-.10	-.04	-.07	-.16	-.11	.10	-.17	-.11
ANTICHOLI-NERGIC MEDICATION	-.08	-.001	-.22	-.13	-.12	.25	-.13	-.23	-.06	.15	-.17	-.26
	d2 test (Errors)				d2 test (Response times)			
	T1	T2	T3	T4	T1	T2	T3	T4
PANSS POSITIVE	.50*	-.02	.19	.21	-.10	.32	.02	.06
PANSS NEGATIVE	-.08	.02	-.19	-.37	.21	.25	-.05	.24
ESRS PARKINSON	-.06	.15	-.06	-.04	.38*	.10	.19	.15
ANTICHOLI-NERGIC MEDICATION	-.09	-.004	.20	-.07	-.15	.06	.12	.10

Figure captions

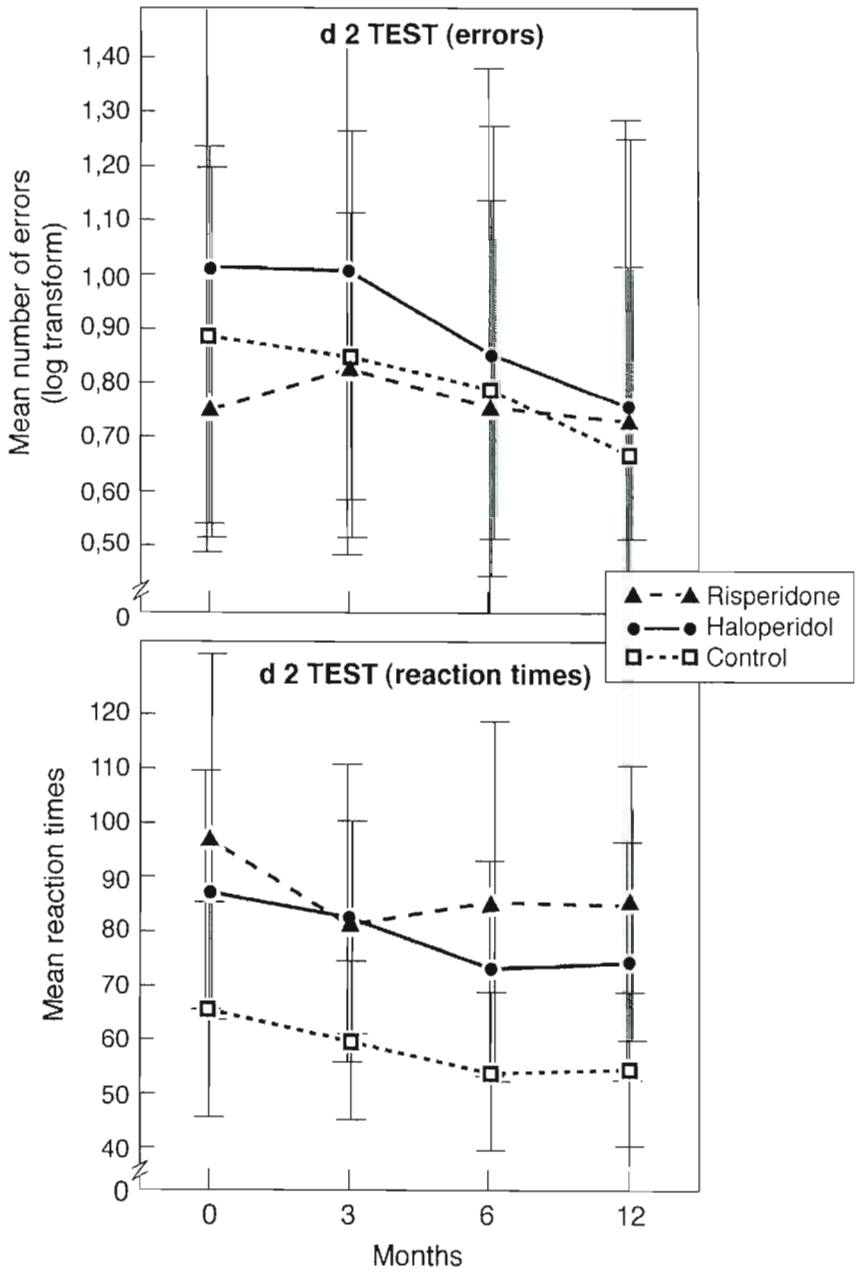
Figure 1. Mean performance scores on CVLT over time for risperidone, haloperidol, and control participants.

Figure 2. Mean performance scores on d2 Cancellation Test over time for risperidone, haloperidol, and control participants.

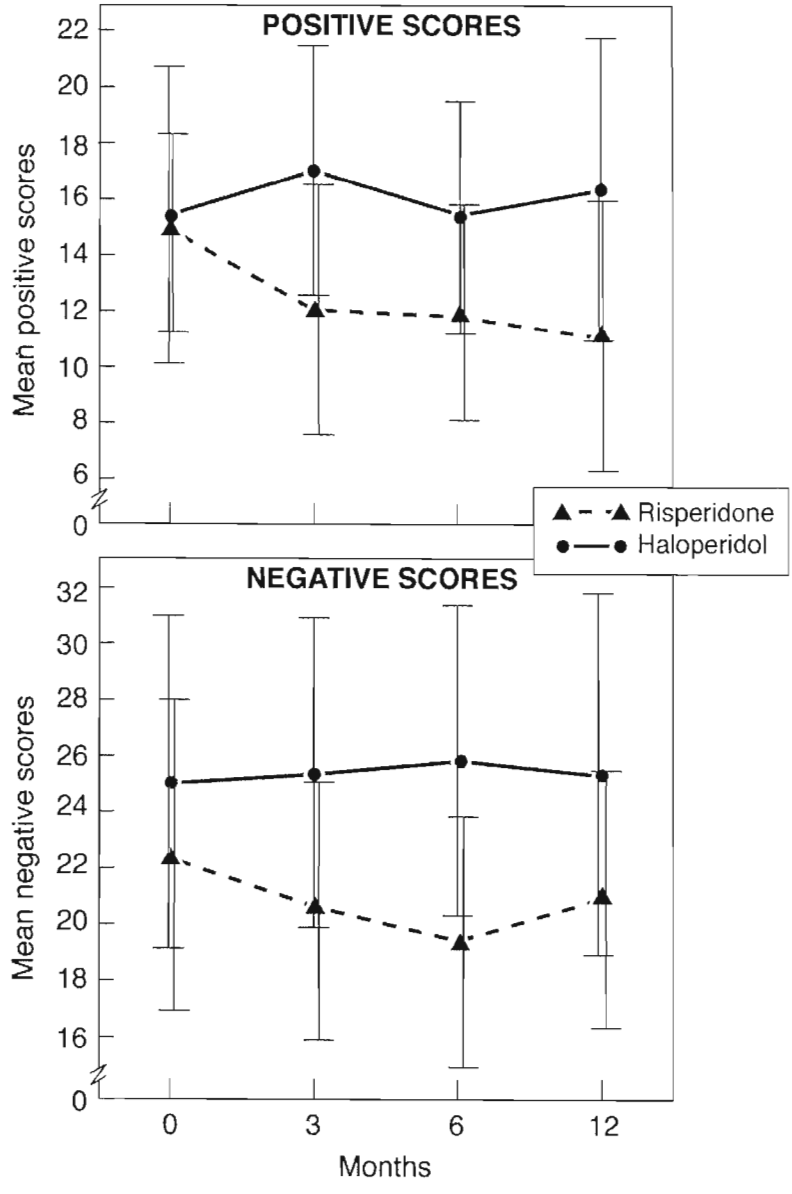
Figure 3. Mean scores on PANSS over time for risperidone and haloperidol treatment groups.



4.11.3 Figure 1. Mean performance scores on CVLT over time for risperidone, haloperidol, and control participants.



4.11.4 Figure 2. Mean performance scores on d2 Cancellation Test over time for risperidone, haloperidol, and control participants.



4.11.5 Figure 3. Mean scores on PANSS over time for risperidone and haloperidol treatment groups.

TROISIÈME ARTICLE

Rémillard, S., Pourcher, E., Cohen, H. (2010). Longterm skill proceduralization in schizophrenia. *Journal of the International Neuropsychological Society, 16,* 148-156.

Le but de cette étude était de déterminer l'effet de la rispéridone (2-6mg) et de l'halopéridol (2-40mg) sur l'apprentissage procédural. Une tâche de lecture en miroir incluant des pairs de mots associés selon un degré de complexité sémantique différent a été administrée à 0, 3, 6 et 12 mois. La performance d'un groupe de 26 schizophrènes, 13 traités avec rispéridone et 13 traités avec halopéridol, a été comparée à la performance d'un groupe de 18 participants sains. Contrairement au groupe contrôle, tous les participants schizophrènes montrent une réduction marquée de la vitesse de lecture en miroir. De plus, l'apprentissage procédural s'est avéré plus affecté par le groupe de participants schizophrènes traités avec halopéridol que ceux traités avec rispéridone. Ces résultats suggèrent qu'une dysfonction de la mémoire procédurale n'est pas inévitablement une composante inhérente de la maladie, mais reflète possiblement l'effet délétère de l'halopéridol sur le striatum. Enfin, les résultats montrent aussi que les deux groupes de schizophrènes ont un profil d'apprentissage similaire à celui du groupe contrôle en ce qui a trait à l'amorçage sémantique intégré à cette tâche de lecture en miroir. Cette dernière observation constitue une évidence que l'accès au réseau sémantique des patients schizophrènes est préservé.

Longterm skill proceduralization in schizophrenia

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3 tables; 2 figures

4.12 Abstract

Previous studies had revealed no specific effect under haloperidol (typical) and risperidone (atypical) neuroleptic (NLP) treatments for schizophrenia (SZ) on a variety of neurocognitive functions relying on the dopaminergic meso-cortico-limbic system. Considering the affinities of D_2 receptors for typical and atypical NLPs, these drugs may differentially affect the functions of the striatum — a determinant brain structure involved in procedural learning. The influence of risperidone (2-6mg) and haloperidol (2-40mg) on a procedural task involving semantically related pairs of words with inverted letters was investigated in this double blind study. The performance of 26 patients with SZ, randomly assigned to risperidone or haloperidol, was compared to that of 18 healthy controls at baseline, 3, 6, and 12 months. All patients with SZ exhibited slower reading speed of the word pairs at all assessment periods and learning was more impaired in the haloperidol- than in the risperidone-treated group. In contrast to SZ patients, healthy controls showed steady improvement in reading speed over the 12 months of the study. However, all SZ participants in the study showed near normal learning profiles from exposure to semantic associations embedded in the procedural memory task, providing evidence for the preservation of associative connections in the semantic network of these patients.

Keywords: Procedural learning; Mirror reading; Implicit memory; Semantic priming; Neuroleptics; Striatum; Risperidone; Haloperidol.

4.13 Introduction

Although dysfunction in the area of explicit memory has been widely reported in patients with schizophrenia (SZ; e.g., Aleman et al., 1999; Cirillo & Seidman, 2003) there have been more conflicting results in studies of procedural learning (PL) in SZ. This type of learning is the ability to gradually acquire new or unfamiliar motor, cognitive or perceptual skills through repeated exposure to a specific rule-governed activity (Cohen & Squire, 1980). Some studies have shown preserved PL in patients with SZ (Clare et al., 1993; Perry et al., 2000; Takano et al., 2002) while others have revealed that these patients are impaired in the acquisition of such skills (Gimenez et al., 2003; Schwartz et al., 1996).

The basal ganglia appear to play a determinant role in PL, based on lesion evidence and neuroimaging studies. Much of the evidence comes from studies of neurodegenerative disorders involving the striatum, such as Huntington's (HD) and Parkinson's diseases (PD) that have been associated with multiple PL deficits (Butters et al., 1985; Cohen & Pourcher, 2007; Harrington et al., 1990; Joel et al., 2005; Martone et al., 1984). More specifically, the involvement of the striatum in motor learning and in mirror reading tasks has been revealed in neuroimaging studies (Poldrack et al., 1998, 1999). Other cortical and cerebellar sites are also involved but their contributions vary widely depending on the learning phase and on the motor and cognitive processes recruited for the task (e.g., Grafton et al., 1992).

Considering the different affinities of D_2 receptors for typical and atypical neuroleptics (NLPs), these drugs may differentially affect the functions of the striatum — a determinant brain structure involved in PL. Haloperidol, a common typical NLP, has higher D_2 dopamine receptor blockade in the striatum, while atypical NLPs administered at a therapeutic dose (such as clozapine, quetiapine, risperidone or olanzapine) are associated with either transient or quantitatively less effective D_2 blockade according to D_2 binding displacement PET studies (e.g., Kapur

et al., 2000). In contrast to haloperidol, risperidone is characterized by greater affinity for serotonin $5HT_{2A}$ than dopamine D_2 receptors and by a less powerful D_2 blockade in associative and sensorimotor parts of the striatum at equivalent antipsychotic dosages. These properties have been related with a favorable extrapyramidal symptoms (EPS) profile and less striatal dysfunction (Kapur et al., 1995).

The investigation of motor PL in SZ has shown that performance is differentially affected under typical or atypical NLP treatment (Bédard et al., 2000; Scherer et al., 2004). Such effects have been revealed between olanzapine and haloperidol treatments on the proceduralization of a visuomotor skill using the Computed Visual Tracking Task; participants under olanzapine performed as well as control subjects, while those treated with haloperidol showed deficits in the acquisition of this skill (Paquet et al., 2004). The influence of three neuroleptic treatments has also been investigated using another type of visuomotor PL task, the mirror drawing task (Scherer et al., 2004). The authors observed that haloperidol-treated patients showed both a disturbed PL and a poor average performance, while risperidone-treated patients showed only poor average performance. Risperidone and clozapine-treated patients showed PL profiles similar to control subjects'. The differential effect of haloperidol, risperidone and olanzapine on cognitive aspects of PL has also been examined in SZ. Performance on the Tower of Toronto test under these drugs was maintained after six weeks but declined after six months under risperidone and haloperidol treatments (Purdon et al., 2003), suggesting that the impairment in PL seen in SZ may be a consequence of neuroleptic-induced dysfunction of the striatum (e.g., Schwartz et al., 1996).

To date, most of the studies investigating the effects of typical and atypical NLPs on the acquisition of a procedural skill have involved a motor component. Few studies have investigated nonmotor aspects of proceduralization in SZ, and those that have

used the mirror-reading task did not take the pharmacological effects into account (e.g., Clare et al., 1993; Takano et al., 2002). Moreover, these investigations were cross-sectional studies or conducted over a short period of time, reporting preserved mirror-reading skill learning in patients with SZ treated with conventional NLPs (Takano et al., 2002). Such experiments do not inform about the effect of treatment over longer time periods.

Impairment in semantic memory – knowledge of the world, facts, concepts and the meaning of words (Tulving, 1972) – has also been frequently shown in SZ using a wide variety of semantic processing tasks (e.g., Al-Uzri et al., 2004; McKay et al., 1996). Degraded representations in the semantic memory store (e.g. Rossell & David 2006) or difficulty in accessing an intact semantic memory (Allen et al., 1993; Joyce et al., 1996) are two proposed mechanisms for this impairment in SZ. According to the network model of semantic memory, each concept is represented as a node in a network, with properties of the concept interconnected through links with related concept nodes. Thus, semantic priming is frequently used for evaluating the degree to which associations between representations stored in semantic memory are intact. There are, however, contradictory results regarding semantic priming effects within SZ. Some have reported abnormal semantic priming for patients with SZ (Gouzoulis-Mayfrank et al., 2003; Moritz et al., 2002; Quelen et al., 2005; Spitzer et al., 1993), while others have shown comparable semantic priming between patients with SZ and healthy controls (Besche-Richard et al., 2005; Blum & Freides, 1995).

In this perspective, the objectives of the present study were to (1) determine the extent to which typical and atypical drugs affect nonmotor aspects of PL in SZ relative to the performance of a healthy control group, (2) assess whether the ability to learn a new perceptual procedural skill is differentially affected by type of treatment over time, and (3) further investigate the semantic aspects involved in mirror reading with patients with SZ.

4.14 Method

4.14.1 Participants

Twenty-six outpatients with SZ participated in the study. The diagnosis was made by a psychiatrist and fulfilled all the criteria of the DSM-IV for SZ. One group of 13 patients (9 men; 4 women) was treated with risperidone, while another group of 13 patients (11 men; 2 women) received haloperidol medication. Over the course of the study, three patients (two patients from the haloperidol treatment group and one patient from the risperidone group) did not complete the last assessment at 12 months because of noncompliance with their treatment. The mean age of the participants, age at diagnosis, duration of psychiatric illness on treatment, and level of education were not statistically different between the two patient groups (all p's > 0.05). A group of 18 healthy volunteers were matched by age and education to the groups of patients in the study. This control group had no history of psychiatric or neurological disorder and was not under psychoactive medication. None of the participants had a history of drug or alcohol abuse. The demographic and clinical characteristics of each group are presented in Table 1. All participants gave their written informed consent prior to their inclusion in the study. The study was carried out according to the principles laid down in the Helsinki declaration and was approved by the ethics committee of the local institution.

---------- Insert Table 1 about here ----------

4.14.2 Tests and procedure

Participants were followed over a period of 12 months and the study included clinical and neuropsychological testing at baseline, 3, 6 and 12 months of treatment. The first assessment was conducted at baseline, when all the 26 participants with SZ were on a stable regimen of haloperidol. After the first assessment, they were randomly assigned to remain on current haloperidol treatment or to follow a switch from conventional NLP to risperidone over a 4-week washout period. In the switching

group, the baseline dose of conventional drug followed a 25% decrease each week until the dose reached 0 mg and a weekly progressive titration of risperidone of 0.5 mg BID, 1 mg BID, 1.5 mg BID, 2 mg BID with a further adjustment of 0.5 mg once or twice a day if judged clinically advantageous. The same psychiatrist consultant administered all the patients' medications. Most of the participants reached the final dosage at 4 weeks and all were stabilized within 8 weeks. A steady state of NLP treatment was maintained over one year.

For the duration of the study, the experimenter was blind to the participants' medication and psychopathological status, while the clinician assessing psychopathology and EPS was blind to their cognitive performance and medication status.

Procedural learning ability was assessed at each assessment session, using a computer-controlled test designed to obtain a measure of acquisition and automatization competence for novel procedures (here reading ability). This test was the same as the one used by Cohen and Pourcher (2007) with PD patients. The PL test was preceded by practice with six pairs of words with inverted letters (not repeated in the experimental test to avoid repetition priming effects) in order to familiarize the participants with the reading task. In the experimental task, words were presented in pairs with vertically rotated letters and there were four blocks of 24 word pairs each. The words were between four and seven letters, in Arial font. Each pair was preceded by a 500 ms fixation cross at the center of a 38 cm screen. The word pairs subtended an angle of 4-5 degrees on either side of the fixation point, with subjects sitting 40 cm away from the screen. The word pairs belonged to one of four types of semantic categories: typical semantic associations from the same category (C1; e.g., table-chair), typical non-semantic associations from different categories (C2; e.g., chair-canary), atypical semantic associations (C3; e.g. ostrich-penguin), and atypical non-semantic associations (C4; e.g., ostrich-whaler). All items in the test

were taken from Brosseau and Cohen (1996). The four types of semantic categories were equally represented within the blocks.

Subjects were required to read as fast and as accurately as possible the word pairs with inverted letters. Time to read aloud each word pair was the time taken from the appearance of the stimulus pair on screen, immediately following presentation of the fixation point, until the last syllable of the second word in the pair was uttered. There was a 2 s interval between word pairs' presentations. All subjects were assessed in the same manner with the same tests, 3, 6 and 12 months later. Speed of response, i.e., reading aloud the word pairs, was measured. Degree of psychopathology was also assessed with the Positive and Negative Syndrome Scale (PANSS; Kay & al., 1989) and extrapyramidal symptoms with the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al., 1980).

4.14.3 Data analysis

An alpha level of .05 was used for all statistical tests. Three sets of analyses were conducted. First, data from the PL task were analyzed using a repeated measures analysis of variance (ANOVA) with Group (Risperidone, Haloperidol, Control) as between-subjects factor. The repeated measures variables were Time (baseline, 3, 6, 12 months) and Procedural learning (mean average reading times for the first and last blocks of word pairs). In order to determine whether the semantic aspects of the task influenced performance, an ANOVA was carried out using Group (Risperidone, Haloperidol, Control) as between-subjects factor, and Time (baseline, 3, 6, 12 months) and Semantic priming (C1, C2, C3, C4) as repeated variables. ANOVAs with Group (Risperidone, Haloperidol) and Time (baseline,endpoint), with repeated measures on the second factor, were conducted to examine the differential effects of both NLP treatments on EPS (parkinsonism, akathisia, dystonia, and dyskinesia). All analyses were performed on transformed (inverse) data.

Contrast analyses were conducted on each significant main effect of Group, in order to determine which group, if any, differed from the other groups (SZ vs. control; risperidone vs. haloperidol). Contrast analyses were also performed on every significant main effect of Time, in order to determine when an improvement occurred (baseline, 3, 6, and 12 months). The Statistical Package for Social Sciences II (SPSS) software was used for all analyses. The Greenhouse-Geisser correction was used in the analysis of the semantic priming data as the sphericity assumption was violated.

4.15 Results

4.15.1 Procedural learning

As eight participants with SZ under haloperidol treatment and two under risperidone were also treated with anticholinergic medication, correlation (PPMC) analyses were first conducted to determine the extent of association between dosage of anticholinergic medication and performance measures of procedural learning in these 10 patients. All correlations were nonsignificant, indicating that there was no association between mirror-reading skill and anticholinergic medication. The correlation values are presented in Table 2.

---------- Insert Table 2 about here ----------

A main effect of Group was observed for the reading performance of inverted word pairs ($F_{(2,41)}$=8.6, p=0.001, Eta-Squared (η^2)=0.30). Contrast analysis was conducted to determine which group differed from the others and showed that overall performance of the patients with SZ was significantly poorer than that of control subjects ($F_{(2,41)}$=13.95, p=0.001, η^2 =0.25). Further contrasts revealed no significant difference between the reading performance of the haloperidol- and risperidone-treated groups ($F_{(2,41)}$=3.21, p=.008, η^2 =0.07).

A main effect of Procedural learning ($F_{(1,41)}$=171.16, p<0.0001, η^2=0.81) was observed, indicating that all participants read words at a faster rate on the last block as they gained experience with reading the word pairs with inverted letters. A main effect of Time ($F_{(3,123)}$=74.98, p<0.0001, η^2=0.65) was also observed, showing that the participants got significantly better at reading the word pairs over the successive assessment periods.

Two interactions were also revealed. First, a Group x Procedural learning interaction ($F_{(2,41)}$=5.09, p=0.01, η^2=0.20) indicated that mirror reading performance was not equivalent for the three groups. Further analyses revealed that only the patients with SZ under haloperidol treatment performed worse than controls ($F_{(1,29)}$=8.99, p=0.006, η^2=0.24 and $F_{(1,29)}$=2.44, p=0.129, η^2=0.08 for the comparisons with healthy controls and Risperidone group, respectively). Second, a Group x Time ($F_{(6,123)}$=2.22, p=0.045, η^2=0.10) interaction indicated that improvement between the four testing sessions was not equivalent for all groups. Contrast analyses revealed that only control subjects showed continual improvement at each assessment [from baseline to 3 months ($F_{(1,17)}$=35.36, p<0.0001, η^2=0.68); from 3 to 6 months ($F_{(1,17)}$=28.049, p<0.0001, η^2=0.62); and from 6 to 12 months ($F_{(1,17)}$=13.809, p=0.002, η^2=0.45)], showing offline learning. The performance of the risperidone-treated group improved from baseline to 3 months ($F_{(1,12)}$=6.009, p=0.031, η^2=0.33) and from 3 to 6 months ($F_{(1,12)}$=15.133, p=0.002, η^2=0.56). No further improvement was shown between 6 and 12 months ($F_{(1,12)}$=0.794, p=0.391, η^2=0.06). A similar outcome was also observed for the haloperidol-treated group ($F_{(1,12)}$=14.136, p=0.003, η^2=0.54; $F_{(1,12)}$=21.8, p=0.001, η^2=0.65 and $F_{(1,12)}$=1.455, p=0.251, η^2=0.11).

Finally, ANOVAs on the number of errors showed no main effects ($F_{(2,41)}$=0.961, p=0.391, η^2=0.05; $F_{(3,123)}$=1.085, p=0.358, η^2=0.03; $F_{(3,123)}$=1.89, p=0.135, η^2=0.04 for the main effect of Group, Time, and Errors, respectively) and no interactions ($F_{(6,123)}$=1.523, p=0.176, η^2=0.07 and $F_{(6,123)}$=0.603, p=0.727, η^2=0.03 for the Group

by Time and for the Group by Errors interactions, respectively) indicating that the accuracy of response was equivalent for the three groups of subjects at all assessment periods. Figure 1 shows the reading performance of each group at each assessment period.

----------Insert Figure 1 about here----------

4.15.2 Semantic priming

ANOVAs on the reading of word pairs belonging to categories with different semantic associations (C1, C2, C3, and C4) showed a main effect of Group ($F_{(2,41)}$=7.82, p=0.001, η^2=0.28). Contrasts revealed no difference between the two patients groups ($F_{(2,41)}$=2.73, p=0.106, η^2 =0.06). However, their performance was poorer than that of control subjects ($F_{(2,41)}$=12.98, p=0.001, η^2 =0.24).

A strong effect of Semantic priming ($F_{(3,123)}$=130.61, p<0.0001, η^2=0.76) was obtained. Contrast analyses showed a significant difference in the time taken to read the word pairs made up of typical exemplars from the same category (C1) and the time to read atypical exemplars drawn from different categories (C4), indicating that the degree of semantic proximity impacts on reading time. For all subjects, pairs of words with closer semantic proximity were read faster. A main effect of Time ($F_{(3,123)}$=101.182, p<0.0001, η^2=0.71) was also shown, indicating that the participants got significantly better from baseline to 3 months ($F_{(1,41)}$=48.447, p<0.0001, η^2=0.54) and from 3 to 6 months ($F_{(1,41)}$=86.907, p<0.0001, η^2=0.68). Performance remained stable until the 12-month assessment period ($F_{(1,41)}$=1.66, p=0.205, η^2=0.04). There was no Group by Semantic priming interaction ($F_{(6,123)}$=1.492, p=0.186, η^2=0.07) and no Group by Time interaction ($F_{(6,123)}$=1.839, p=0.097, η^2=0.08), suggesting that the patient groups appeared to benefit from the semantic proximity effect just as much as the control subjects over the course of the study. Figure 2 shows the performance of

the three groups of participants in reading pairs of words with varying degrees of semantic proximity.

----------Insert Figure 2 about here----------

4.15.3 Long-term effects of neuroleptic treatment on extrapyramidal symptoms

ANOVAs showed a significant effect of Group ($F_{(1,24)}$=10.512, p=0.003, η^2=0.31), with the haloperidol-treated group showing higher dyskinesia symptom scores. A main effect of Time ($F_{(1,24)}$=11.924, p=0.002, η^2=0.33) and a significant Group by Time interaction ($F_{(1,24)}$=10.717, p=0.003, η^2=0.31) indicated a differential evolution of dyskinesia symptoms under these two treatments, with haloperidol showing higher symptom scores at the end of the study ($F_{(1,12)}$=0.016, p=0.903, η^2=0.001 and $F_{(1,12)}$=23.353, p<0.0001, η^2=0.66 for risperidone and haloperidol, respectively). An ANOVA for Parkinsonism symptoms revealed a Group by Time interaction ($F_{(1,24)}$=7.698, p=0.011, η^2=0.24), also suggesting a treatment-dependent effect on the evolution of this EPS over time. Contrast analysis showed that risperidone was more effective ($F_{(1,12)}$=5.743, p=0.034, η^2=0.32) than haloperidol ($F_{(1,12)}$=2.308, p=0.155, η^2=0.16) in reducing Parkinsonism symptoms from baseline to endpoint. There was no significant effect of Group ($F_{(1,24)}$=1.914, p=0.179, η^2=0.07) or Time ($F_{(1,24)}$=2.962, p=0.098, η^2=0.11) for Parkinsonism EPS.

ANOVAs on dystonia and akathisia scores revealed no difference between the two groups of patients with SZ ($F_{(1,24)}$=0.17, p=0.684, η^2=0.01 and $F_{(1,24)}$=0.224, p=0.641, η^2=0.01 for dystonia and akathisia, respectively), no change in scores over time ($F_{(1,24)}$=1.796, p=0.193, η^2=0.07 and $F_{(1,24)}$=0.137, p=0.714, η^2=0.01) as well as no interaction between Group and Time ($F_{(1,24)}$=1.128, p=0.299, η^2=0.05 and $F_{(1,24)}$=0.189, p=0.668, η^2=0.01). This suggests that the severity and change in dystonia and akathisia symptoms over time were equivalent for the two treatment groups. Table 3 presents the evolution of EPS scores.

----------Insert Table 3 about here----------

4.16 Discussion

In this study, we attempted to determine the long-term effects of neuroleptic drug treatments on non-motor procedural learning in patients with SZ treated with typical (haloperidol) or atypical (risperidone) medication. Our results showed that all participants had the capacity to acquire new procedural skills necessary for the reading of words with inverted letters, as evidenced by faster reading times by the end of each testing session. However, a significant slowing of reading time was shown in both treatment groups relative to healthy controls. Moreover, haloperidol patients performed worse on mirror-reading relative to the risperidone-treated patients and healthy controls.

The differential effects of typical haloperidol and atypical risperidone on the striatum D_2 receptors may explain these observations and suggest that nonmotor PL dysfunction is, in part, reversible in the course of SZ. In contrast to healthy controls that showed steady improvement over each assessment period, both NLP-treated groups reached a plateau halfway through the study in their capacity to improve mirror-reading skill.

Our observations add weight to the evidence that the striatum is not only essential for the acquisition of a new motor procedural skill, but is also involved in the learning of non-motor procedural skills, as is the case with mirror reading tasks. The results also indicate that patients with SZ under haloperidol medication show more pronounced learning disturbances. Treatment with risperidone showed lower incidence of EPS Parkinsonism and dyskinesia in contrast to haloperidol. Risperidone possesses mixed serotoninergic and dopaminergic antagonist properties that renders it more protective than typical NLPs in the correction of adverse motor side effects (Peusken, 1995). Lower EPS have been associated with less striatal dysfunction (Kapur, 1995), which

strongly suggests that the better mirror-reading performance under risperidone treatment is to some extent the result of less striatal D_2 receptor occupancy. This view is in accord with results from a number of studies. For example, response speed in a PL task was facilitated with an indirect dopamine agonist (d-amphetamine) and inhibited with an antagonist (haloperidol) in healthy subjects (Kumari et al., 1997). One hypothesis to explain the mechanism by which haloperidol impacts on cognitive function and, in this case, in the acquisition of procedural routines is via higher striatal dopamine D_2 receptor occupancy. For example, Corripio et al. (2004) showed that D_2 receptor occupancy was higher in patients treated with haloperidol (approx. 75%) than with patients treated with an atypical neuroleptic (ziprasidone; approx. 60%) at equivalent antipsychotic dosage. The atypical property linked to the coexistence of a $5HT_2/D_2$ may provide relative protection from extrapyramidal syndromes (Kapur et al., 1995) and mixed blockade may be less deleterious for striatal motor as well as non motor functions.

The patients on haloperidol were given anticholinergic medication to correct for motor extrapyramidal side-effects. It has been reported that anticholinergic drugs may have a deleterious effect on cognitive functions (e.g. Vinogradov et al., 2009). However, the poorer learning performance observed in the haloperidol group is not explained by the use of anticholinergic medication, as there was no significant relationship between this concurrent drug treatment and procedural learning performance over the duration of the study. This adds weight to the assumption that this type of learning is more likely modulated by striatal dopaminergic systems. It should be noted that the pharmacology of procedural learning is still in its infancy and additional investigations are required before we can confidently dissect the respective involvement of dopamine and the striatum in skill acquisition in patients with SZ.

The present study also investigated the contribution of the semantic associations embedded in a procedural memory task. As was the case with the control subjects, mirror-reading speed improved with degree of semantic association for all patients in the two treatment groups. Greater semantic proximity within a word pair was associated with faster reading time. These observations provide evidence for the preservation of associative connections in the semantic network of patients with SZ and generally agree with findings reporting equivalent semantic priming effects in patients with SZ and healthy controls (e.g., Quelen et al., 2005). However, they are at odds with studies showing abnormal heightened automatic spread of activation within semantic networks (e.g. Gouzoulis-Mayfrank et al., 2003). Factors such as diagnostic category may explain these differing observations. The patients in the present study included essentially paranoid and a few residual types of patient with SZ, while other studies showing hyperpriming effects were conducted with thought-disordered patients with SZ (e.g., Moritz et al., 2002; Spitzer et al., 1993). As unimpaired semantic priming with thought-disordered patients has also been observed (Besche-Richard et al., 2005; Blum & Freides, 1995), the variability in results across studies may also be task-specific and related to methodological issues, including direct vs. indirect priming, lexical decision vs. word naming tasks, as well as duration of the interstimulus interval (e.g., Kreher et al., 2008).

In a previous study (Rémillard et al., 2008), impairment on a verbal declarative memory task (the California Verbal Learning Test; CVLT; Delis et al., 1987) had been shown with the same two groups of patients who took part in this study. The patients recalled significantly fewer items on the CVLT and used inadequate semantic clustering strategies to hold information in memory. Taken together, these observations suggest that the access to semantic memory systems under implicit processing (priming effect) is apparently intact in SZ, while more intentional processing of information, such as using a specific semantic categorization strategy to learn and recall new information, is impaired. To date, there is no consensus

regarding the nature of the semantic deficits in SZ. However, our results agree with others that have shown difficulty in accessing an intact semantic memory in patients with SZ (Allen et al., 1993; Joyce et al., 1996) rather than a degraded semantic knowledge store (e.g. Rossell & David 2006). The generalization of our findings is, however, made with caution and there is need for further replication with designs using both implicit and explicit measures of semantic memory within the same sample of patients.

4.17 Conclusion

Our earlier investigations of long-term effects of NLP drug treatment on cognitive function in patients with SZ have shown that haloperidol and risperidone do not differ in their impact on a variety of neurocognitive functions, such as executive function, attention and verbal episodic memory (Rémillard et al., 2005, 2008). The present findings clearly show that there is, however, a specific and differentiating effect between these two drugs on the patients' ability to proceduralize a cognitive task. These results indicate a deleterious effect of the conventional drugs on striatal function in contrast to the effect produced by atypical medication. The results also highlight the need to maintain so called atypical drugs such as olanzapine and risperidone in the low range of posology, where D_2 striatal blockade lies under a safe therapeutic range for extrapyramidal symptoms in order to preserve new habit learning in young schizophrenic patients. The findings also reveal, indirectly, the primary role of dopaminergic processes in the acquisition of procedural memory.

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4.17.1 Table 1: Baseline demographic and clinical characteristics of participants

	Risperidone $n = 13$	Haloperidol $n = 13$	Control $n = 18$	Statistical results
Sex (men: women)	9:4	11:2	11:7	
Mean age, yr (SD)	40.5 (10.4)	48.9 (9.1)	41.2 (9.5)	ns
Mean education, yr (SD)	12.2 (3.2)	11 (2.9)	13.4 (2.6)	ns
Mean age at Diagnosis, yr (SD)	26.3 (7.2)	28.8 (9.4)		ns
Mean duration of haloperidol NLP treatment before study enrollment, yr (SD)	15.7 (11.2)	20.7 (6.8)		ns
Mean NLP dosage, *mg/day* (SD)	4 (1.4)	13 (10)		
Range of NLP doses	2-6 mg/day	2-40 mg/day		
Mean anticholinergic dosage, *mg/day (SD)*	0.29 (0.84)	1.8 (1.97)		* $p < 0.05$
Number of patients receiving anticholinergic / n	2/13	8/13		
PANSS positive	16.6 (3.6)	16.9 (5.5)		ns
PANSS negative	21.8 (5.2)	25.7 (6)		ns
ESRS parkinsonism	16.7 (10.3)	13.5 (9.1)		ns
ESRS dystonia	0.7 (2.2)	0.4 (0.7)		ns
ESRS dyskinesia	1.5 (2.4)	0.6 (0.9)		ns
ESRS akatisia	0.8 (1.4)	0.2 (0.4)		ns

* $p < 0.05$; ** $\chi^2 < 0.05$

4.17.2 Table 2: Correlations between procedural learning measures and anticholinergic dosage

	Baseline		3 months		6 months		12 months	
	Block 1	**Block 4**	**Block 1**	**Block 4**	**Block 1**	**Block 4**	**Block 1**	**Block 4**
PPMC	.114	.259	-.147	-.046	.231	.078	-.122	.182
p	0.753	0.471	0.686	0.889	0.407	0.783	0.737	0.614

4.17.3 Table 3: Mean extrapyramidal symptom scores

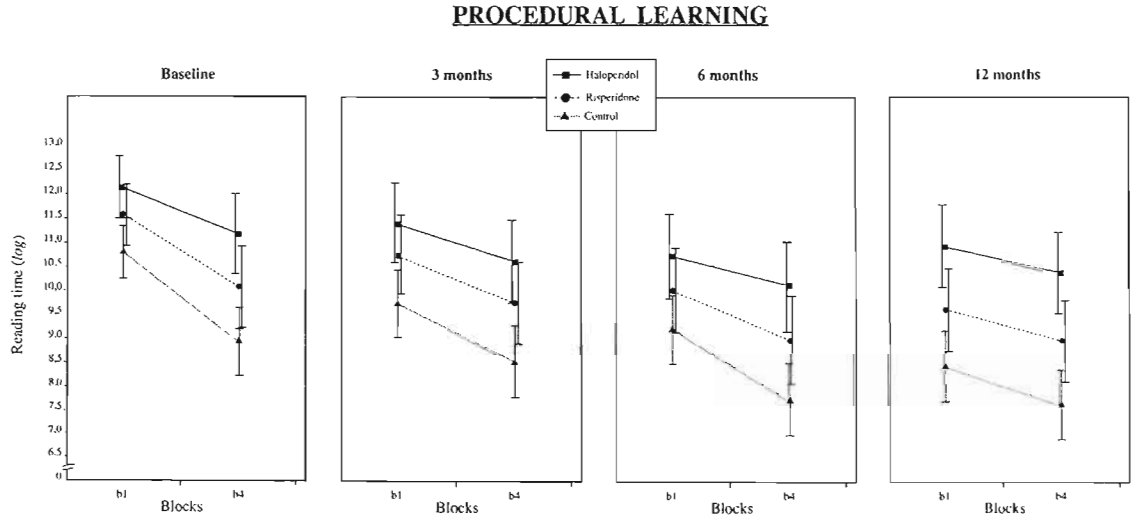
	Parkinsonism		Dyskinesia		Akathisia		Dystonia	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Risperidone	1.13 (0.25)	* 0.84 (0.53)	0.17 (0.30)	0.18 (0.24)	0.08 (0.23)	0.07 (0.25)	0.10 (0.27)	0.11 (0.26)
Haloperidol	1.11 (0.28)	1.18 (0.24)	0.16 (0.25)	** 0.66 (0.28)	0.08 (0.23)	0.15 (0.45)	0.10 (0.19)	0.18 (0.24)

* $p < 0.05$; ** $p < 0.0001$

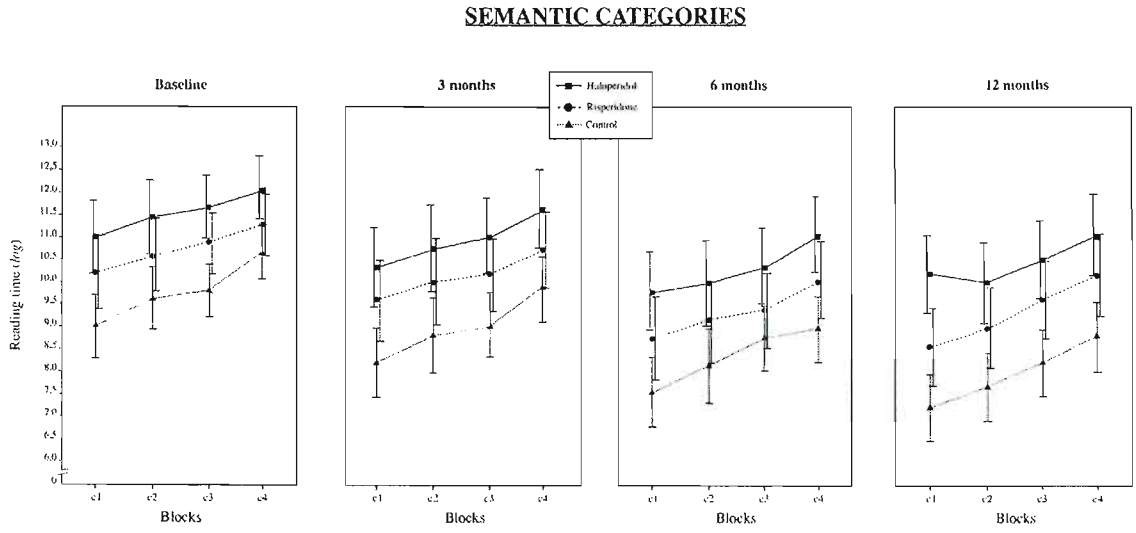
Figure captions

Figure 1. Mean reading times (95% confidence interval) taken by risperidone, haloperidol and control groups to read the pairs of words with inverted letters (blocks 1 and 4) at each assessment period.

Figure 2. Mean reading times (95% confidence interval) taken by risperidone, haloperidol and control groups to read pairs of words differing in semantic proximity at each assessment period. (C1: high typicality exemplars from the same category; C2: high typicality exemplars from different semantic categories; C3: low typicality exemplars, same category; C4: low typicality exemplars, different categories).



4.17.4 Figure 1



4.17.5 Figure 2

CHAPITRE V

DISCUSSION GÉNÉRALE

INFLUENCE DES NEUROLEPTIQUES TYPIQUES ET ATYPIQUES SUR LA SYMPTOMATOLOGIE CLINIQUE ET SUR LES FONCTIONS COGNITIVES

5.1 Traitement neuroleptique et symptomatologie clinique

Les travaux de cette thèse ont permis de déterminer l'effet différentiel de la rispéridone (affinité plus élevée pour les récepteurs $5HT_{2A}$ que pour les récepteurs D_2) et de l'halopéridol (forte affinité pour les récepteurs D_2) sur les fonctions cognitives et sur la symptomatologie clinique sur une période de 12 mois. Le degré de sévérité des symptômes psychopathologiques et extrapyramidaux avait été évalué à l'aide de la PANSS et de l'ESRS, respectivement. On a comparé les scores obtenus à ces deux échelles par des groupes de patients schizophrènes chroniques traités à la rispéridone ou à l'halopéridol. Les résultats montrent un effet supérieur de la rispéridone dans l'amélioration des symptômes négatifs de la schizophrénie ainsi que de certains SEPs – parkinsonisme et dyskinésie. Le traitement NLP classique, à halopéridol, ne montre pas de tels effets.

Il est possible que l'effet antagoniste des récepteurs sérotoninergiques $5HT_{2A}$ ait agi sur les symptômes négatifs de la SZ, ce qui cadrerait indirectement avec l'hypothèse d'une hypodopaminergie frontale dans ce trouble du comportement. Il a été montré que l'action antagoniste des récepteurs sérotoninergiques facilite la libération de dopamine dans les aires corticales préfrontales (Pehek, 1996). Ainsi, les propriétés pharmacologiques qui distinguent les NLPs atypiques des NLPs typiques expliqueraient la réduction des symptômes négatifs observés chez les patients traités à

la rispéridone. Par opposition, le groupe traité avec un NLP typique ne montre pas une telle amélioration des symptômes négatifs de la maladie; ceci serait probablement dû au fait que cette médication NLP ne démontre pas d'affinité pour les récepteurs sérotoninergiques de type $5HT_{2A}$. Ces résultats vont dans le même sens que ceux obtenus par d'autres études comparant les effets thérapeutiques de la rispéridone et de l'halopéridol (Bondolfi et al., 1998; Conley & Mahmoud, 2001; Peusken, 1995; Rabinowitz & Davidson, 2001; Yen, Lung & Chong, 2004).

Bien que la rispéridone et l'halopéridol possèdent des propriétés pharmacologiques distinctes, il demeure difficile de caractériser l'effet direct de l'action antagoniste $5HT_{2A}$ sur les symptômes négatifs primaires d'une diminution des symptômes négatifs secondaires (induits par une dépression, une anxiété ou des effets iatrogènes extrapyramidaux). Une plus faible induction de SEP observée sous traitement de rispéridone peut avoir contribué de façon significative à l'amélioration des symptômes négatifs.

On peut aussi considérer que les différences remarquées dans les effets de ces traitements sur la symptomatologie clinique soient le résultat de la dose utilisée. Les études menées par Nyberg, Nilsson, Okubo, Halldin et Farde (1998) ont montré qu'un blocage de plus de 80 % des récepteurs D_2 striataux entraîne des SEP. Il a aussi été montré qu'une dose de 2 mg, 4 mg et 6 mg de rispéridone provoque un taux d'occupation dopaminergique D_2 striatal de 66 %, 73 % et 79 %, respectivement (Kapur, 1995), tandis qu'une dose d'halopéridol de plus de 4 mg par jour provoquerait plus de 80 % de blocage des récepteurs dopaminergiques striataux (Kapur, Roy, Daskalakis, Remington & Zipursky, 2001). Or, les groupes de schizophrènes qui ont participé à la présente étude ont reçu en moyenne une dose de 4 mg de rispéridone (intervalle de 2 à 4 mg) comparativement à une dose moyenne de 12 mg d'halopéridol (intervalle de 2 à 40 mg).

Une posologie plus modérée de NLP classique aurait provoqué moins d'effets iatrogènes, et le groupe de patients traités à l'halopéridol aurait peut-être montré une évolution de la symptomatologie semblable à celle du groupe traité au NLP atypique. Cependant, il reste qu'une faible dose d'halopéridol (5 mg) a une efficacité semblable à un traitement de 6 mg de rispéridone en ce qui a trait à l'évolution des symptômes positifs et négatifs sur une période de 2 ans (Marder et al., 2003). Dans cette dernière étude, la rispéridone s'est avérée plus efficace que l'halopéridol sur le plan de la dépression, de l'anxiété et des SEP. Outre l'aspect primaire ou secondaire de la symptomatologie qui demeure difficile à distinguer, les propriétés antagonistes des récepteurs $5HT_{2A}$ et D_2 semblent responsables de l'efficacité supérieure de la rispéridone à traiter les symptômes négatifs.

5.2 Traitement neuroleptique et fonctions cognitives

Les travaux présentés ici ont principalement permis de déterminer l'effet à long terme des traitements à la rispéridone et à l'halopéridol sur la cognition — l'attention, les fonctions exécutives, la mémoire épisodique verbale et l'apprentissage procédural — de patients SZ chroniques comparés à un groupe de sujets contrôles. Dans l'ensemble, tous les sujets schizophrènes ont eu des performances semblables aux tâches de mémoire verbale, d'attention et de fonctions exécutives (tâches qui mettent à contribution le système dopaminergique méso-cortico-limbique), quel que soit le traitement reçu. Par comparaison avec le groupe contrôle, les deux groupes de patients SZ ont été plus lents dans la tâche d'attention visuelle sélective, et ont montré un déficit de la mémoire épisodique verbale et des fonctions exécutives. Par contre, des différences entre les deux traitements NLP ont été observées pour ce qui est des fonctions cognitives qui mettent à contribution le système dopaminergique nigrostrié. Dans une tâche de lecture en miroir, un apprentissage de type procédural, les patients sous traitement typique ont eu des performances plus faibles que ceux sous traitement atypique.

Il a donc été remarqué qu'il n'y a aucune différence entre ces deux formes de traitement sur les fonctions cognitives qui dépendent de l'intégrité des aires cérébrales préfrontales. Ces résultats vont à l'encontre d'études qui avaient montré une supériorité de la rispéridone sur l'halopéridol pour les fonctions exécutives (Cuesta et al., 2001; Harvey, Green, McGurck & Meltzer, 2003). Cependant, la méthodologie de l'étude présentée ici est plus rigoureuse que celles couramment notées dans la littérature et caractérisées par l'absence d'un groupe contrôle de sujets sains (e.g., Cuesta et al., 2001) ou qui portaient sur une durée relativement courte (e.g., 8 semaines; Harvey et al., 2003).

Les présents résultats ne confirment pas qu'il y a une diminution des dysfonctions cognitives suite à l'effet antagoniste sur les récepteurs sérotoninergiques $5HT_{2A}$ — qui distinguent les NLPs atypiques des NLPs typiques. Pehek (1996) avait montré qu'il y a une augmentation de dopamine dans le cortex préfrontal suivant l'injection de ritansérine (un antagoniste sérotoninergique de type 5HT2) chez le rat. Or, chez l'homme, il est bien possible qu'un taux de dopamine optimal soit nécessaire pour assurer le bon fonctionnement des aires cérébrales préfrontales dans l'accomplissement de tâches complexes et plus exigeantes. Parallèlement, une étude menée par Williams et Goldman-Rakic (1995) sur les récepteurs dopaminergiques de type D_1 préfrontaux va dans le même sens. Cette étude réalisée chez le singe a révélé que la performance à une tâche de mémoire de travail pouvait être modulée en fonction de la dose de SCH 39166 (un antagoniste sélectif des récepteurs D_1). Les auteurs avaient alors conclu à l'existence d'un niveau optimal d'occupation des récepteurs D_1 pour une signalisation physiologique et une performance optimales (Goldman-Rakic, Muly & Williams, 2000). Il est donc possible que l'action antagoniste sérotoninergique de la rispéridone n'ait pas induit une concentration optimale de dopamine pour améliorer le fonctionnement cortical préfrontal chez les patients SZ.

Une autre hypothèse proposée pour expliquer le mécanisme d'action des NLPs atypiques sur l'amélioration de certaines fonctions cognitives avance que les effets observés peuvent être liés à la diminution des symptômes de la SZ, particulièrement la réduction des symptômes négatifs (Hong et al., 2002). Les résultats de l'étude présente indiquent que la rispéridone a un effet réducteur sur les symptômes négatifs de la schizophrénie, mais n'entraine pas une diminution des dysfonctions exécutives telles que mesurées par le WCST. Ces résultats ne s'accordent pas avec l'hypothèse d'une relation entre amélioration de la symptomatologie clinique et des fonctions cognitives qui impliquent les aires corticales préfrontales (Voruganti, Heslegrave & Awad, 1997; Basso, Nasrallah, Olson & Bornstein, 1998). D'autres études ont aussi montré que cette relation supposée entre symptomatologie négative et déficit neurocognitif ne tenait pas (Collins, Remington, Coulter & Birkett, 1997; Hughes et al., 2002). Ainsi, on voit bien que les dysfonctions cognitives semblent indépendantes des manifestations cliniques de la SZ.

Sur le plan de l'apprentissage procédural, par comparaison avec le groupe contrôle, les schizophrènes ont montré une performance globale plus faible au test de lecture en miroir, quelque soit le traitement NLP reçu. Comme la rispéridone et l'halopéridol agissent sur les récepteurs dopaminergiques D_2 nigrostrié, ces observations reflètent probablement l'implication du striatum dans l'apprentissage d'une tâche de lecture en miroir et vont dans le même sens que les études d'imagerie cérébrale (Poldrack, Desmond, Glover & Gabrieli, 1998; Poldrack, Prabhakaran, Seger & Gabrieli, 1999).

Par comparaison avec le groupe contrôle, les résultats ont aussi montré une meilleure performance dans l'apprentissage d'une tâche de lecture en miroir sous traitement à la rispéridone que sous traitement NLP classique. Un taux d'occupation des récepteurs D_2 striataux plus élevé sous halopéridol que sous rispéridone a été

observé (Kapur, 1995; Kapur et al., 2001) ce qui peut vraisemblablement expliquer la différence des performances obtenues ici.

Il est possible que l'action antagoniste $5HT_{2A}$ de la rispéridone ait favorisé le fonctionnement de la voie dopaminergique nigrostriée. Puisque la sérotonine inhibe la libération de dopamine, il a été supposé que le blocage des récepteurs sérotoninergiques $5HT_{2A}$ des NLPs atypiques aurait le potentiel d'augmenter la libération de dopamine dans le striatum. Ce mécanisme serait responsable d'une atténuation des effets du blocage D_2 sur cette voie et par conséquent induirait moins de SEP. Ces résultats vont dans le sens des études qui ont montré un effet différentiel des NLPs typiques et atypiques sur l'apprentissage procédural de patients schizophrènes (Bédard et al., 2000; Paquet et al., 2004; Purdon et al., 2000; Scherer et al., 2004).

Bien que le mécanisme d'action des NLPs atypiques sur l'apprentissage procédural ne soit pas clairement établi, les résultats de la présente étude ont montré que l'action antagoniste $5HT_{2A}/D_2$ de la rispéridone exerce un effet moins délétère sur le striatum – meilleure performance au test d'apprentissage procédural et induction moindre de SEP – que la composante pharmacologique de l'halopéridol.

5.3 CONTRIBUTION DE CETTE THÈSE

Les travaux reliés à cette thèse ont contribué à déterminer l'efficacité à long terme des NLPs atypiques sur le fonctionnement cognitif des schizophrènes chroniques. Ces informations sont déterminantes afin de mieux intervenir sur le plan clinique et de faire le meilleur choix de traitement pour les personnes atteintes de SZ.

L'apport original des travaux de cette thèse repose sur l'inclusion d'un groupe contrôle sain et sur l'évaluation des effets à long terme du traitement NLP. Ils ont

permis de voir que la rispéridone, un NLP atypique, n'exerce pas d'effet supérieur à un traitement NLP classique (l'halopéridol) sur les fonctions cognitives mettant à contribution les systèmes dopaminergiques méso-cortico-limbiques. En revanche, la rispéridone montre un effet thérapeutique clinique supérieur, ce qui pourrait prédisposer les patients schizophrènes à un meilleur apprentissage procédural. Les généralisations des travaux antérieurs sur les effets des neuroleptiques typiques et atypiques, qui n'avaient pas pris en compte d'évaluer les performances cognitives de patients à celles de sujets contrôles sains, sont limitées dans leur portée et posent problème. Il en va de même avec les travaux qui n'ont étudié que les effets d'une seule drogue à la fois ou l'effet à court terme de ces traitements. Ainsi, les chercheurs qui se penchent sur les effets des NLPs sur les fonctions cognitives doivent prendre en compte ces facteurs méthodologiques non négligeables afin de tirer des conclusions plus justes.

Différents médicaments sont prescrits au cours de l'âge adulte et du vieillissement pour traiter diverses maladies psychiatriques ou neurologiques, comme la dépression, l'anxiété, les démences ou la maladie de Parkinson. Les travaux de cette thèse mettent en évidence un constat fondamental soit l'importance d'étudier l'impact pharmacologique des médicaments sur la cognition. Connaître l'effet délétère ou supérieur des médications qui agissent au niveau du système nerveux central est primordial, car le maintien de l'autonomie dans les activités de la vie quotidienne, ainsi que les activités sociales et professionnelles reposent sur un fonctionnement optimal des processus cognitifs.

5.4 LES LIMITES DE CETTE ÉTUDE

Certains aspects des travaux présentés dans le cadre de la thèse peuvent, à certains égards, contraindre la portée des conclusions tirées ici. Par exemple, il aurait été souhaitable qu'il y ait eu un plus grand nombre de participants. En effet, même si

la taille des effets statistiques est acceptable, de modérée à élevée, de nombreuses études qui s'intéressent à des sujets connexes comportent des échantillons de sujets plus nombreux. Il faut cependant mentionner que la plupart d'entre elles ne portent pas sur une durée de 12 mois.

Les doses d'halopéridol administrées aux patients de l'étude constituent un autre aspect à considérer. En effet, les doses administrées étaient élevées, bien qu'adéquates du point de vue clinique au moment où l'étude a été menée, au début des années 2000. Les travaux ultérieurs qui porteront sur l'effet différentiel des NLPs typiques et atypiques devraient avoir recours à de faibles doses de NLP typiques, car l'impact sur le fonctionnement du striatum dépend directement de la quantité administrée: une dose de NLP typique de plus 4 mg bloquerait plus de 80 % des récepteurs dopaminergiques striataux et entrainerait l'apparition de SEP (Farde et al., 1996; Kapur et al., 1999). Ainsi, la comparaison des doses relativement équivalentes en terme de degré de saturation des récepteurs D_2 striataux aiderait à préciser dans quelle mesure la manifestation des SEP est comparable entre ces classes de NLPs. À l'inverse, si le degré de sévérité des effets neurologiques indésirables diffère de la même façon entre les deux groupes de NLPs, il serait alors possible de conclure à un rôle direct de l'action antagoniste sérotoninergique $5HT_{2A}$ dans l'amélioration de la symptomatologie négative primaire de la schizophrénie.

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